Synthetic Explorations and Expeditions in the Resveratrol Class

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ABSTRACT

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Chapter 1. The Chemistry and Biology of Resveratrol-Derived Natural Products

Research interest in resveratrol, a structurally simple plant metabolite, has increased exponentially in the last two decades. Since its isolation from red wine it has been hypothesized that this structure may account for the so-called "French Paradox," the notion that despite a diet high in cholesterol one can enjoy a relatively healthy lifestyle through moderate red wine consumption. The biological implications of these claims are presented. Concurrently isolated along with resveratrol are hundreds of oligomeric natural products with structures varying in both size and complexity. The discovery, biosynthesis, and previous synthetic studies towards these natural products will be presented to frame the landscape of the field and its current limitations.

Chapter 2. Total Synthesis of Heimiol A and Hopeahainol D

Heimiol A and hopeahainol D are oxidized, resveratrol dimers characterized by their [3.2.2] bicyclic framework with a bridging ether. The total synthesis of these epimeric natural products was accomplished by the development of a halolactonization/Friedel-Crafts cascade to construct the bicyclic core. Subsequently, a steric bias inherent in the molecule was doubly exploited to synthesize both targets with complete selectivity. During the course of these studies, a number of unexpected results

were observed which have led, or may potentially lead, to alternate courses of investigation. These results and their potential impact are also presented.

Chapter 3. Explorations Into the Construction of 9-Membered Carbocycles: The Total Synthesis of Caraphenol A

Well-established in the synthetic community are the challenges associated with medium-sized ring construction. Of particularly rarity are solutions addressing all carbon 9-membered rings. Seeing this motif present in a subclass of resveratrol oligomers, we sought to investigate this challenging substructure. Our efforts to achieve this end are detailed with the successful development of two unique methods to construct the requisite 9-membered ring core. One succeeded in the first ever reported *9-exo-dig* cyclization while the other enabled the robust total synthesis of caraphenol A.

Chapter 4. [1.1.1]-Orthocyclophanes and the Synthesis of the Elusive Triketone

[1.1.1]-orthocyclophanes have received considerable attention of late due to their numerous applications in the field of supramolecular chemistry. Owing to their rigid, bowl shape, these scaffolds are capable of engaging in numerous guest-host complexes. The previous syntheses of [1.1.1]-orthocyclophanes as well as a survey of their applications are presented. In the course of our synthetic studies toward caraphenol A, we accomplished the synthesis of a unique [1.1.1]-orthocyclophane as well as the successful oxidation to its corresponding triketone. These results are presented noting that despite many efforts, no other [1.1.1]-orthocyclophane triketone has ever been successfully synthesized with our work constituting the first such report.

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LIST OF ABBREVIATIONS

AcOH	acetic acid
HSCoA	coenzyme A
TfOH	trifluoromethanesulfonic acid
Ac_2O	acetic anhydride
HRP	horseradish peroxidase
DPPH	2,2-diphenyl-1-picrylhydrazyl
TFA	trifluroacetic acid
*m*CPBA	*meta*-chloroperoxybenzoic acid
NBS	N-bromosuccinimide
KO*t*-Bu	potassium *tert*-butoxide
IBX	2-iodoxybenzoic acid
p-TSA	*para*-toluenesulfonic acid
BnBr	benzyl bromide
CAN	cerium ammonium nitrate
MsOH	methanesulfonic acid
LiNph	lithium naphthalenide
n-BuLi	*n*-butyl lithium
TBCO	2,4,4,6-tetrabromocyclohexa-2,5-dienone
NBA	N-bromoacetamide
TCCA	trichloroisocyanuric acid
BDSB	bromodiethylsulfonium bromopentachloroantimonate
EtOAc	ethyl acetate

t- BuOH	*tert*-butanol
NMO	*N*-methylmorpholine oxide
NIS	*N*-iodosuccinimide
DMSO	dimethylsulfoxide
TBHP	*tert*-butylhydrogenperoxide
3Å M.S.	3Å molecular sieves
HG-II	Hoveyda-Grubbs 2nd Generation Catalyst
PPA	polyphosphoric acid
TIPS-Cl	triisopropylsilyl chloride
AIBN	Azobisisobutyronitrile
TBDPS-Cl	*tert*-butyldiphenylsilyl chloride
DCE	1,2-dichloroethane
DIAD	Diisopropyl azodicarboxylate
DBU	1,8-Diazabicycloundec-7-ene
MOM-Cl	methoxymethyl chloride
DMF	dimethylformamide
DIBAl-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
KHMDS	Potassium bis(trimethylsilyl)amide
BzCl	benzoyl chloride
PMB-Cl	para-methoxybenzyl chloride
PPTS	pyridinium para-toluenesulfonate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

PREFACE

The vast majority of research to be discussed in this thesis lies in the realm of natural product total synthesis. The studies contained herein will demonstrate not only the power of organic synthesis to deliver highly complex molecular architectures in a creative and efficient manner, but also the ease with which an appropriately designed route can produce natural product analogues, an ability all but absent in synthetic biology. Furthermore, total synthesis has served as a source of inspiration for developments in countless other fields from organic synthetic methodology to materials chemistry, a point also to be discussed and supported in the following chapters.

By its very nature, target oriented synthesis often leads to a limited view on what is or can be achieved in the course of a total synthesis. The tendency to focus only on what progresses to the established final target is great. However, the frequency of unexpected results in the course of pursuing a target is immense as are the discoveries to be found within those unexpected results. The following chapters will also display the value of curiosity towards those unanticipated outcomes and the fruits of pursuing that curiosity.

In particular we will show the problems encountered and the solutions developed towards the total syntheses of a number of resveratrol derived oligomeric natural products. The results of these studies will exhibit the development of new and unique reaction pathways as well as demonstrate the power of in depth conformational analysis toward manipulating complex frameworks. Finally, through careful attention to unexpected outcomes during the course of these synthetic efforts we have made significant contributions outside the realm of the immediate projects.

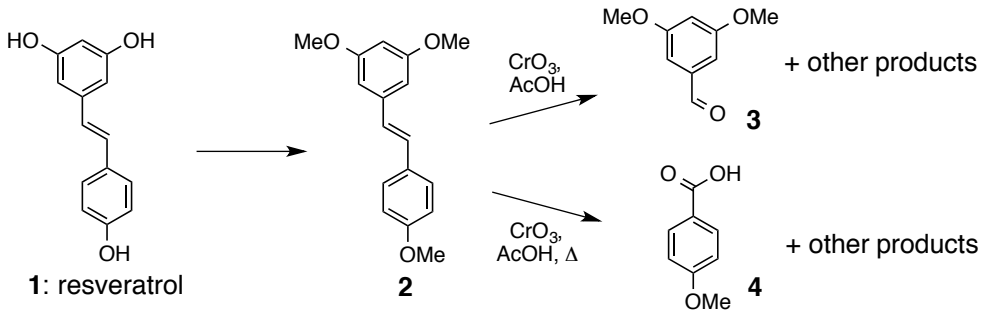
Chapter 1

The Chemistry and Biology of Resveratrol-Derived Natural Products

1.1 Isolation and Structure Determination of Resveratrol

The first mention of resveratrol (**1**) came in a 1939 paper by Michio Takaoka in the *Journal of the Chemical Society of Japan*.[1] In this communication, Takaoka outlined his isolation of a phenolic substance by direct crystallization of the EtOH extracts of the *Veratrum album* variety of *grandiflorum*, a plant with some previous medicinal use, ranging from the treatment of "insanity" to non-specific abdominal cramping,[2] despite its well-established toxicity.[3] After determining the molecular formula of this pure substance by elemental analysis, its structure was

Figure 1. Resveratrol Structure Determination



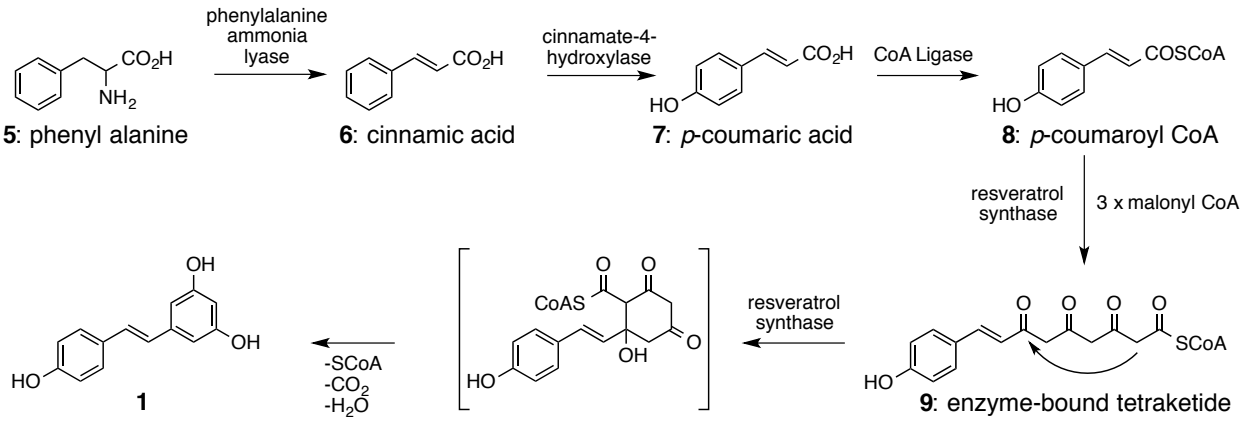
discerned through treatment of resveratrol trimethyl ether (**2**) with CrO_3 in AcOH at room temperature, a reaction which produced 3,5-dimethoxy benzaldehyde (**3**), or in boiling AcOH, an event which produced *p*-anisic acid (**4**) (Figure 1). The identities of these two degradation products were then confirmed by comparison with known samples. The name "resveratrol" for this substance was presumably derived from the presence of a resorcinol ring in combination with its isolation from the genus *Veratrum*.

1.2 Biosynthesis of Resveratrol

The biosynthesis of resveratrol begins with the three-step transformation of phenylalanine (**5**) into 4-coumaroyl-CoA (**8**) as outlined in Figure 2.[4] This sequence proceeds through the oxidative deamination of the starting amino acid, yielding cinnamic acid (**6**), followed by

hydroxylation of its aromatic ring under the action of cinnamate-4-hydroxylase to give **7** and, finally, appendage of the CoA unit. At this point, resveratrol synthase is employed to append three equivalents of malonyl-CoA, extending the substrate into an enzyme-bound tetraketide intermediate (**9**). This material can then undergo cyclization and subsequent aromatization (through the loss of water and CO_2) to generate resveratrol (**1**).[5]

Figure 2. Biosynthesis of Resveratrol



1.3 The Biology of Resveratrol in Plants

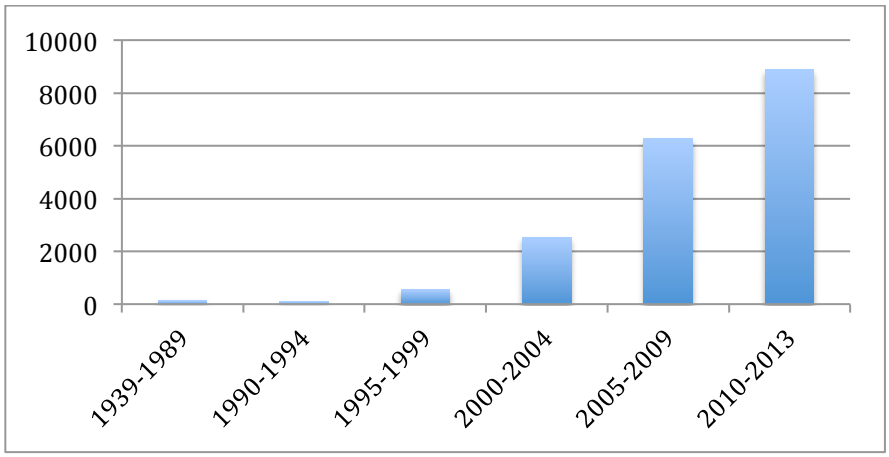
Resveratrol, and its higher order oligomers, are classified as phytoalexins, meaning that they are compounds produced in response to environmental stress. In the context of those plant species which produce it, resveratrol serves as a defense against several negative stimuli including UV radiation,[6] fungal infection,[7] chemical exposure,[8] and wounding of the plant tissue.[9] For instance, in healthy leaves and berries of various *Vitaceae* (grapevine) species, only very low concentrations of resveratrol are typically detected.[10] Upon cultivation with the fungus *Botrytis cinerea* (a commonly encountered fungus for wine grapes), however, resveratrol production increased significantly and was localized at the site of infection.[11] Moreover, a negative correlation was observed between resveratrol production in each species and the

susceptibility of that particular plant to the invading fungus, thus demonstrating that resveratrol is indeed produced as a response to the invading fungus and that it is successful in combating said invasion.[12]

1.4 The Biology of Resveratrol in Animals

In 1992, Siemann and Creasy published a report outlining the presence of resveratrol in wine and suggested that resveratrol may be responsible for some of the cardioprotective effects known to result from moderate wine consumption.[13,14] This cardiovascular benefit, often referred to as "the French Paradox" because people in France live longer despite a diet relatively high in fat and cholesterol presumably due to increased red wine consumption,[15] had been long bereft of an acceptable explanation as the constituents of red wine identified up to that point were widely distributed in other common staples of the average diet. Resveratrol, by contrast, was an exception and, once identified, was advanced as the long sought unique component.[16] With this new finding, research interest into resveratrol and its benefit to human health increased exponentially as demonstrated in Figure 3.

Figure 3. Number of Publications and Patents Mentioning Resveratrol



Perhaps the most intensely studied, and best demonstrated, potential effect of resveratrol *in vivo* is the ability to mimic the positive results of caloric restriction and thus possibly increase life span and combat symptoms generally associated with aging. Initial studies towards this end were conducted in simple organisms such as *Saccharomyces cerevisiae* (yeast), *Caenorhabditis elegans* (nematode worms), and *Drosophila melanogaster* (flies)[17, 18] and yielded very encouraging results with each invertebrate enjoying a significantly increased life span upon receiving a resveratrol-enriched diet. Moving up the ladder of complexity, a short-lived vertebrate fish (*Nothobranchius furzeri*) with an average life span of nine weeks was fed resveratrol as a supplement to its standard diet and, likewise, experienced an increase in both median and maximum lifespan (56% and 59% respectively).[19] Furthermore, these resveratrol-treated fish retained fecundity and experienced a significant delay in neurofibrillary degeneration and loss of cognitive ability, symptoms associated with aging. When similar experiments were conducted in mice, however, the same effects on longevity were not observed.[20] Healthy mice and rats who ate resveratrol-supplemented diets did not experience a statistically significant increase in lifespan. Positive results were observed when high calorie-fed mice were started on resveratrol at midlife. These mice experienced a tempering of the negative symptoms associated with high caloric intake (higher mortality, decreased insulin sensitivity, and decreased motor function) as compared with those mice on the same diet that did not receive resveratrol.[21] Overall, the health of the high calorie fed mice supplemented with resveratrol shifted heavily towards that of mice on a standard diet.

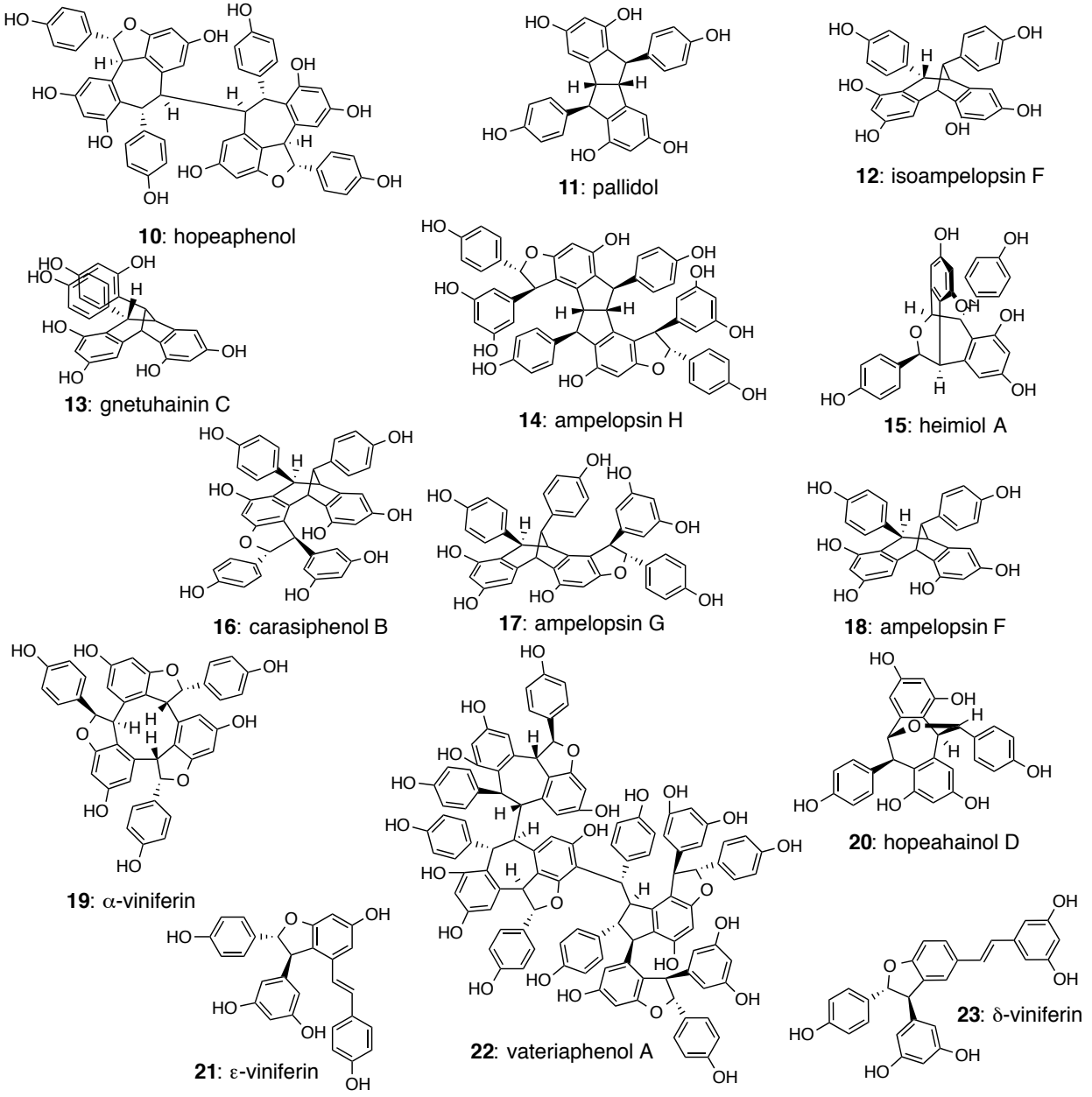
As the evidence and excitement for resveratrol as an age-defying supplement mounted, so too did the drive for understanding the underlying biological mechanisms responsible for such promising results. In the ensuing few years, a general consensus was reached that the desirable

properties of resveratrol consumption in the aforementioned studies was the result of upregulation of the sirtuins,[17] a class of deacetylase proteins affecting numerous cellular processes including aging, metabolic function, and mitochondrial biogenesis, among others.[22] Unclear, though, was the exact manner in which resveratrol activated the pathways that led to increases in sirtuin activity, a debate which remains unsettled today. That mechanistic ambiguity perpetuates because of questions concerning the validity of some of the initial experiments[23] as well as the conflicting reports that sirtuins (SIRT-1 in humans) are activated directly through an allosteric mechanism[24] and/or that their production is indirectly increased through upstream regulation upon exposure to resveratrol.[25] Answers to these questions are critical to the successful development of highly sought after therapeutics capable of combating aging and its associated symptoms. Since the focus of this thesis related to chemical synthesis, a detailed overview of the proposed mechanisms of action and their supporting evidence will not be provided here; suffice it to say, the debate continues and the further investigations will impart a clearer understanding of the role of resveratrol in these complex pathways. What is certain, however, is that resveratrol has spawned immense interest in the sirtuin proteins which has already led to a greater understanding of these critical pathways. Whether directly or indirectly, the discovery of, and investigation into, resveratrol will have a significant impact on future treatment for age-related diseases.

1.5 Higher Order Resveratrol Oligomers and Their Biosynthesis

In addition to isolating resveratrol, natural product chemists have identified, isolated, and characterized a vast structural array of oligomeric natural products derived from resveratrol (Figure 4). While the structure of resveratrol itself is that of a simple stilbene, many of these

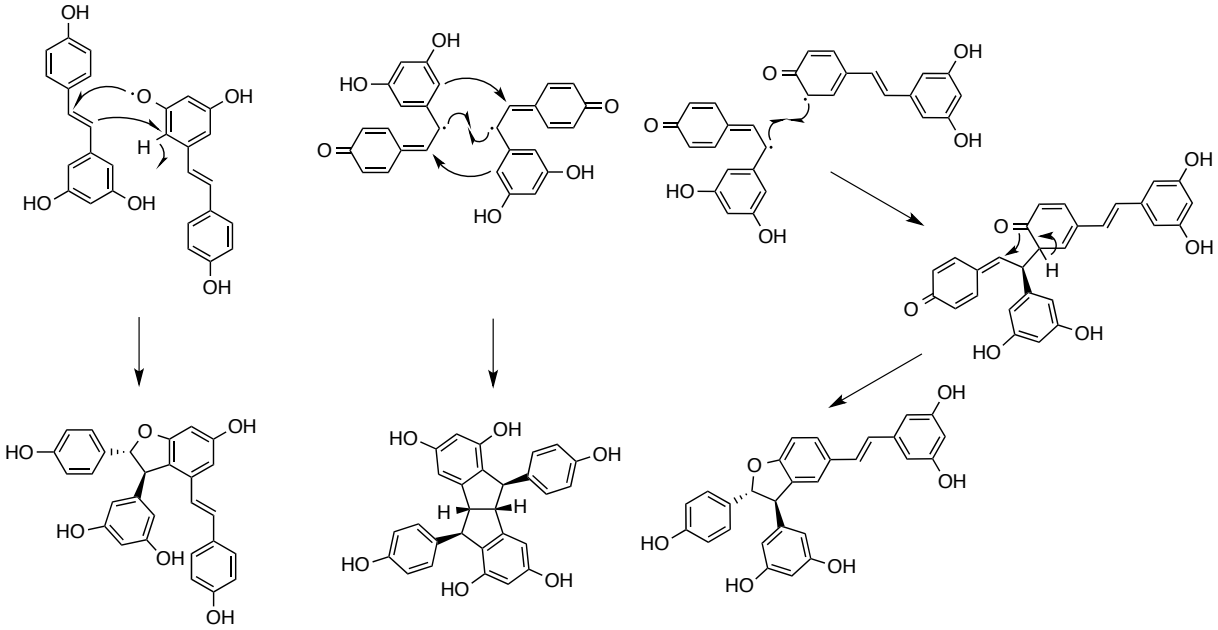
Figure 4. Selected Resveratrol-Based Oligomeric Natural Products



oligomers possess intricate and complex carbon frameworks; an octomeric natural product has even been isolated and characterized (vateriaphenol A, **22**).[26] Following its generation in plant tissues, resveratrol is exposed to peroxidase enzymes, an event that leads to its oxidative dimerization to a number of different frameworks. One hypothesis as to how these diverse dimeric frameworks are generated is that the oxidized resveratrol units combine in various ways

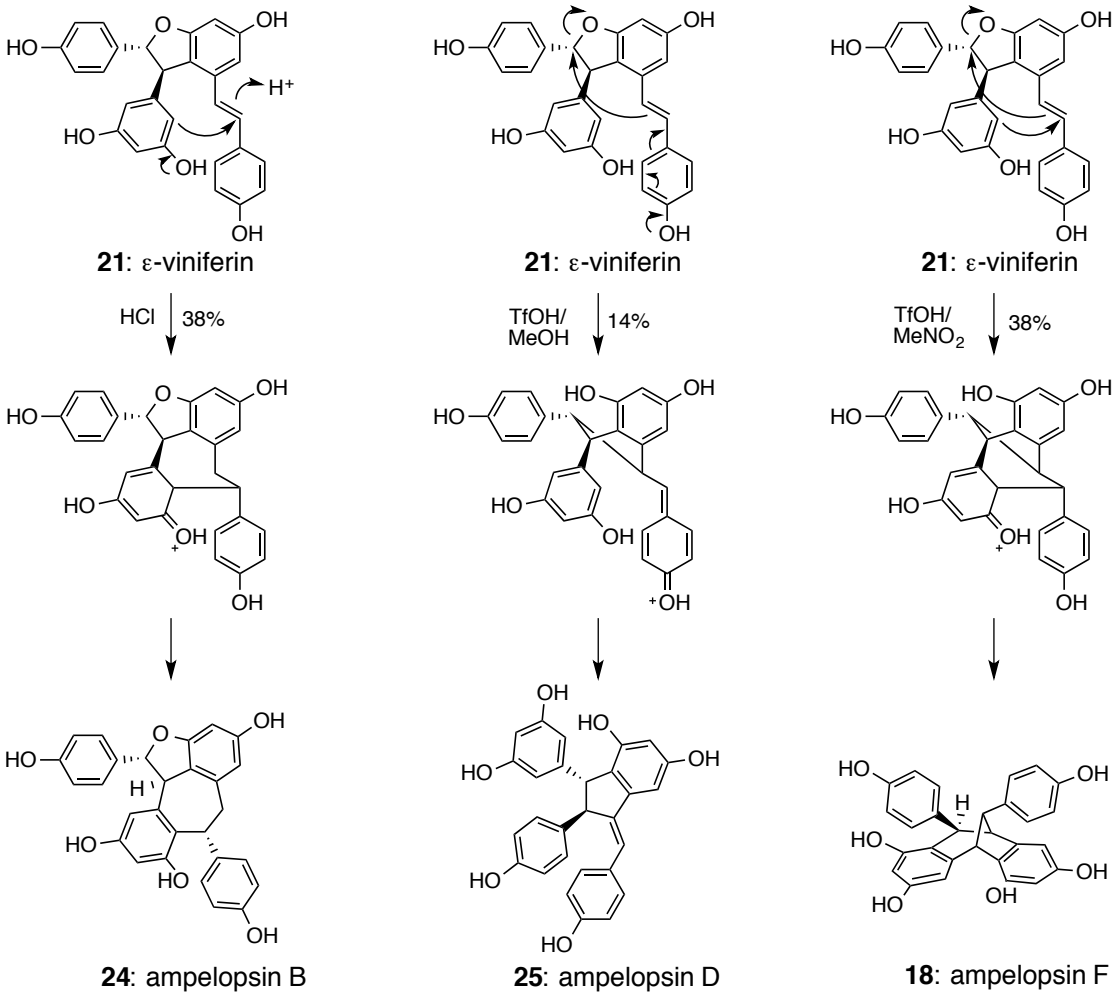
to generate unique scaffolds directly such as δ-viniferin (**23**) or pallidol (**11**) (Figure 5).[27] Another theory postulates that a more complex branching point, such as the dimer ε-viniferin (**21**), is formed first and then undergoes rearrangement to other natural product structures at the

Figure 5. Possible Biosynthesis of Resveratrol Dimers



same oligomer level (see Figure 6). Given the vast structural and stereochemical diversity in the resveratrol natural product family, and the plausibility of both mechanisms toward generating such diversity, it is likely that both are operative. Following dimer biosynthesis, additional monomeric units can be added to the existing scaffolds; this event usually, but not always, takes place in the form of *trans*-disposed dihydrobenzofuran moieties.[27] Even while adding this common motif, the ability to select between several viable sites for its addition onto a single framework (**18** going to **16** or **17**, Figure 4) further amplifies the range of structural diversity.

Figure 6. Biomimetic Rearrangments of Reveratrol Dimers



Given this collection of structures derived from a common monomeric unit, and even stereochemical variation within a single structure (see structures **12**, **13** and **18** with Figure 4; three distinct diastereomers of the same carbon framework), as well as the fact that many of them are isolated together from the same plant tissue, it can be argued that their biosynthesis is somewhat random and/or directed toward the creation of diversity. This supposition is circumstantially supported by the function of these phytoalexin molecules in that it is to the plant's advantage to generate as many structures as possible to combat an unknown invading fungus. Species with the ability to produce such a diverse repertoire quickly would thus hold a potential evolutionary advantage. If true, however, because the vast majority of these resveratrol

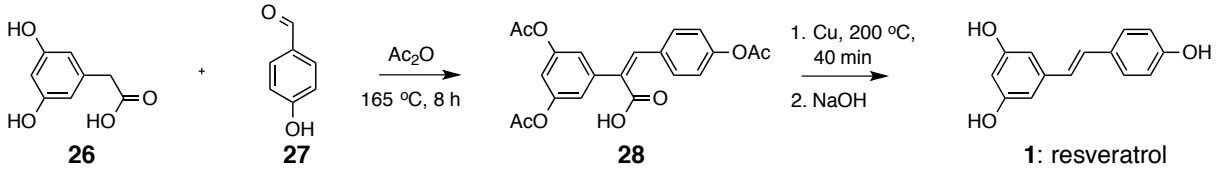
based natural products are isolated in enantiopure form, one would have to reconcile that fact with a hypothesis of random construction since such biosynthetic stereoselectivity suggests enzymatic assistance.[28] In a 2002 review by Cichewicz and Kouzi,[27] the authors postulate that a resveratrol radical generated by one of a few peroxidases known to have affinity for resveratrol is then captured by an "accessory protein," a species which provides a chiral scaffold on which coupling then occurs in enantiopure fashion. The authors note that while this hypothesis is consistent with existing data, it is far from proven and further research is needed to elucidate these mechanisms conclusively. An alternate, and somewhat hybrid theory, between the random and directed hypotheses described above lies in the notion that perhaps a single, or select few, structures are enzymatically produced and they then serve as the chiral branching point for all other members of the family. ε-viniferin (**21**) seems a likely candidate as it is perhaps the most widely distributed resveratrol dimer and a significant number of other resveratrol-based scaffolds are accessible from it based on studies to date. A set of experiments by the Niwa group supports this theory.[Error! Bookmark not defined.] They show the rearrangement of ε-viniferin to ampelopsin B, D, and F under simple acid treatment and that the stereochemical purity of the starting material is not compromised over the course of the transformation (Figure 6). These newly formed products can then, in theory, be elaborated into higher-order oligomers with existing chiral centers directing the installation of new ones.

While resveratrol itself garners little interest from the standpoint of a synthetic chemist, its higher order oligomers possess the structural complexity to pose a formidable synthetic challenge. It is this quality, along with an intriguing array of bioactivity that is uniquely associated with the oligomeric family members (*vide infra*), that has drawn the attention of the synthetic community and inspired a number of creative approaches toward their construction.

1.6 Previous Syntheses of Resveratrol-Based Natural Products

The increased interest in the biological activity and structural complexity of resveratrol and its higher-order oligomers has been accompanied by a rise in research efforts by the organic synthetic community. In the year following his initial isolation report, Takaoka published the first total synthesis of resveratrol (**1**) using an aldol condensation and subsequent decarboxylation of simple starting materials as outlined in Scheme 1.[29] Since this publication, numerous syntheses of resveratrol and its analogues have been reported, focused primarily on the

Scheme 1. Takaoka's 1940 Synthesis of Resveratrol



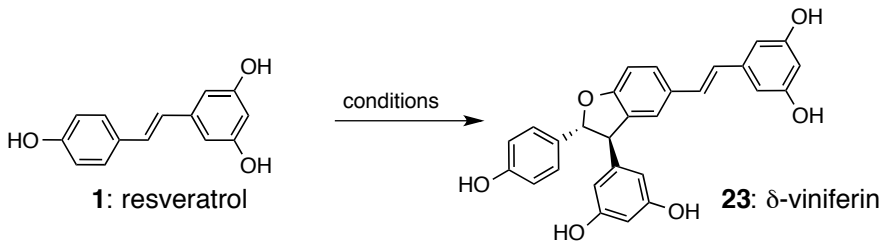
use of the Wittig reaction[30] or Heck coupling,[31] as the key bond-forming event. The first reported structure of an isolated resveratrol oligomer was that of hopeaphenol (**10**, Figure 4) in 1965[32] followed then by α- and ε-viniferin in 1977 (**19** and **21**).[33] While syntheses of resveratrol and its glycosylated derivatives were accomplished as early as 1940, it was not until the 1990s that the synthesis of higher-order resveratrol oligomers become of significant interest. Since then, a number of groups have developed routes towards various natural products in this family. These approaches will now be surveyed beginning with biomimetic strategies followed by retrosynthetically designed approaches. The organization of syntheses presented is chosen based on strategy, and does not necessarily follow a chronological progression.

1.6.1 Biomimetic Approaches

As described earlier, the biosynthesis of resveratrol-based oligomers involves oxidation of resveratrol to a stabilized radical followed by coupling two equivalents of that radical in one

of their various resonance forms (see Figure 5). Given the ease of obtaining resveratrol through standard synthetic methodology, submitting it to enzymatic conditions or various single-electron oxidants presents itself as an obvious approach. The first foray into the laboratory construction of higher-order oligomers through such a design came in 1977 when Langcake and Pryce submitted resveratrol to the influence of horseradish peroxidase (HRP) in the presence of H_2O_2 and obtained a synthetic dimer in 41% yield.[34] This molecule was later isolated and classified as a natural product and ultimately given the name of δ-viniferin (Scheme 2).[35] Numerous other oxidants and conditions (DPPH, laccasse, AgOAc, COX-1, $FeCl_3$/acetone, MnO_2, HRP in basic conditions)[36] selectively delivered the same product in yields of up to 97%.

Scheme 2. Biomimetic Dimerization of Resveratrol to δ-Viniferin



1: resveratrol **23**: δ-viniferin

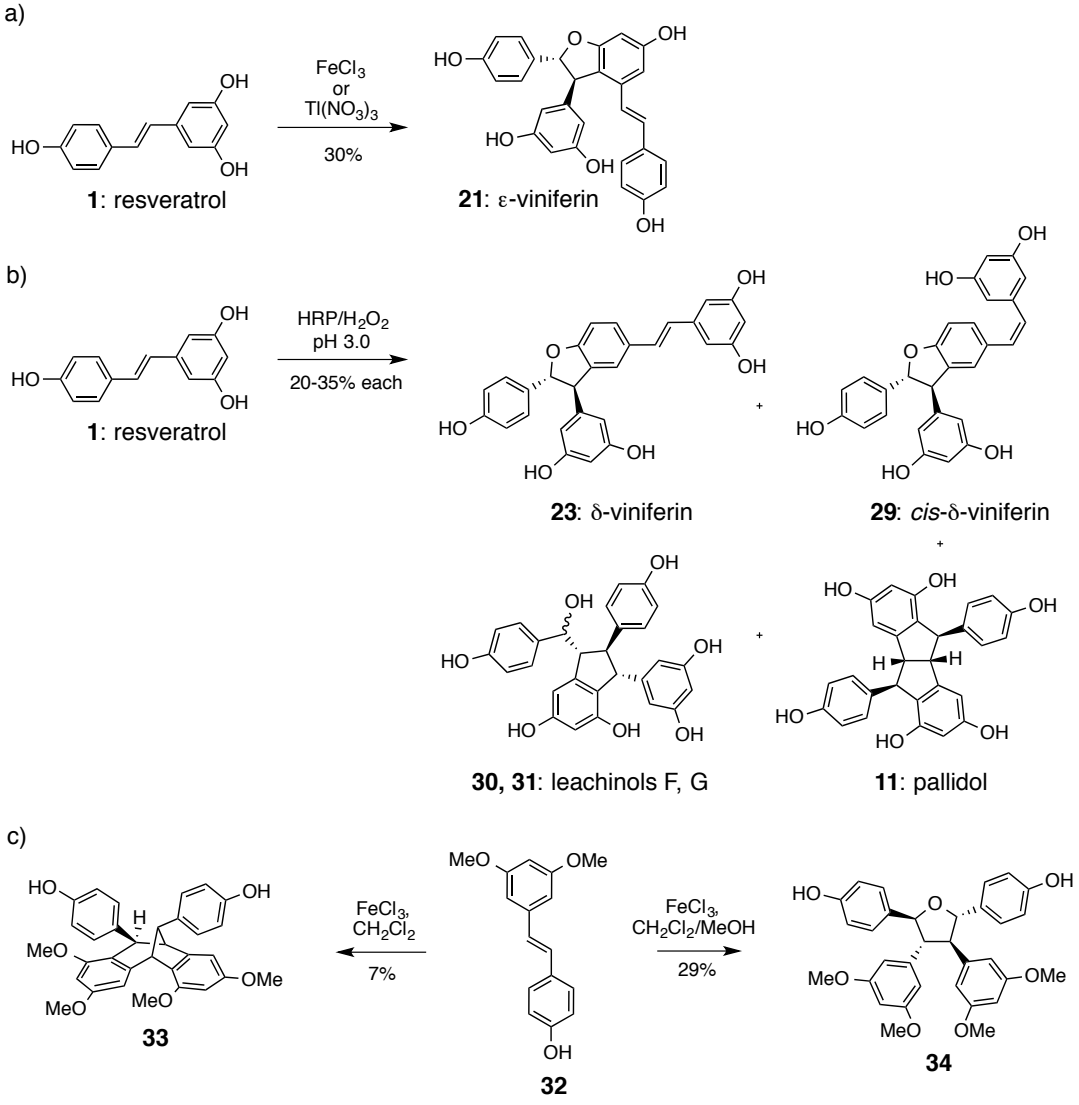
Entry	Oxidant	Solvent	Temperature	Time	Yield
1	HRP/H_2O_2	Acetone/H_2O	20 °C	1 h	41%
2	DPPH	MeOH	25 °C	30 min	18%
3	*M. Thermophyl* laccasse	*n*-Butanol/pH 6.5 buffer	45 °C	4 days	31%
4	AgOAc	MeOH	50 °C	1 h	97%
5	$COX\text{-}1/H_2O_2$	pH 8.0 buffer	25 °C	10 min	-
6	$FeCl_3$	Acetone	25 °C	20 h	97%
7	MnO_2	CH_2Cl_2	25 °C	24 h	91%
8	HRP/H_2O_2	Acetone/pH 8.0 buffer	-	-	93%

Such selectivity for a single product can be rationalized by its formation from two resveratrol radicals generated on the *para*-substituted ring of resveratrol (See Figure 5). Unlike a radical generated on one of the *meta*-substituted phenols, the *para*-substituted phenol radical benefits from the stabilization of the adjoining double bond, thus making its formation more favorable.

The prevalence of two of these stabilized radicals coupling in such a manner so as to preserve aromaticity in all four aromatic rings of the product then comes as no surprise.

Due to thorough investigations and screening, chemists have uncovered conditions capable of generating other dimeric and trimeric natural products in a biomimetic fashion with moderate selectivity as well. Under the influence of $FeCl_3$ or $Tl(NO_3)_3$ in MeOH, preference can be observed for ε-viniferin (**21**), as shown in Scheme 3a, delivering the product in 30% yield, along with approximately 40% and 56% of recovered starting material respectively and no other

Scheme 3. a) Biomimetic Synthesis of ε-Viniferin. b) Effect of pH on Oxidative Dimerization. c) Effect of Partial Protection on Oxidative Dimerization

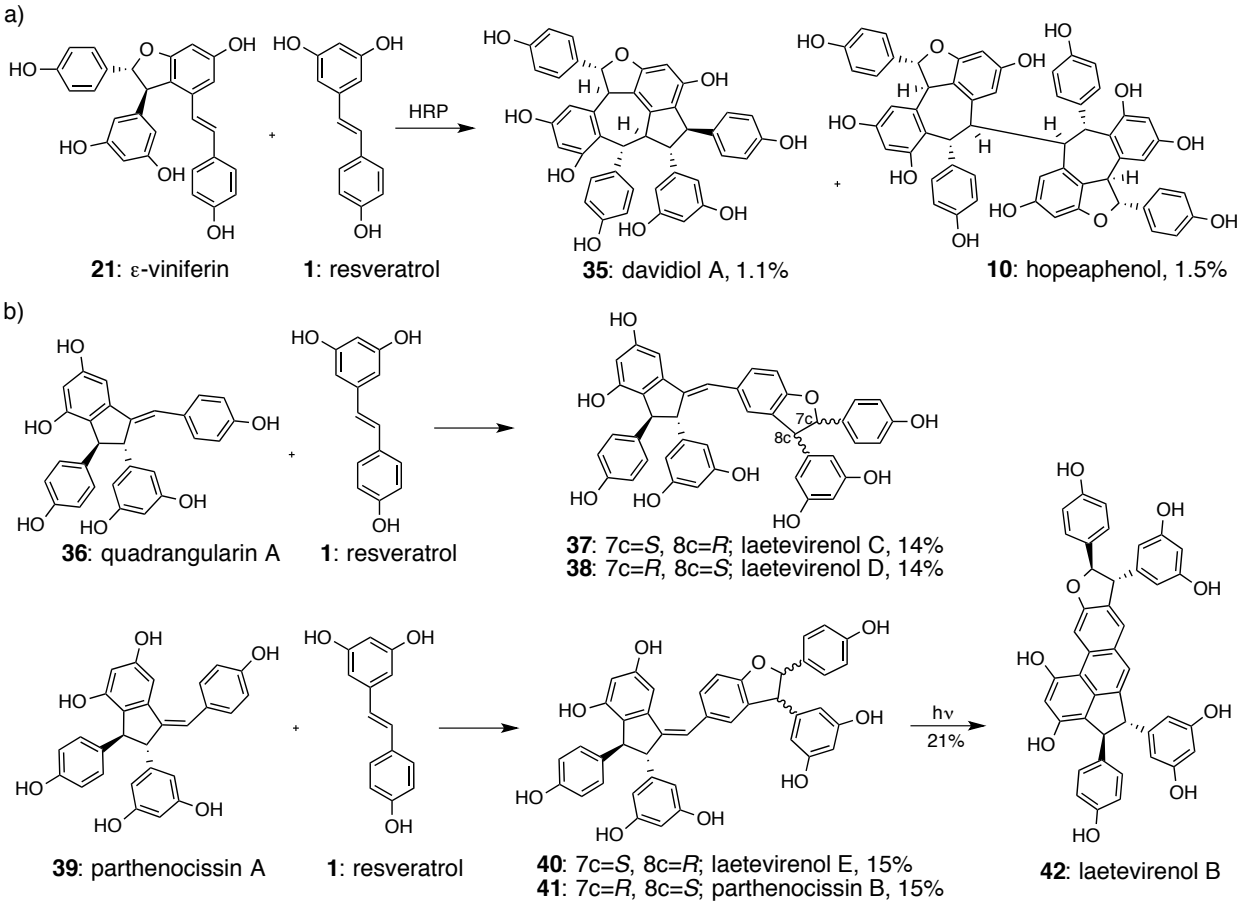


dimeric products isolated.[37,36e] An interesting study was published detailing the effects of pH on the results of horseradish peroxidase oxidation of resveratrol in 2012. Though excellent selectivity was only obtained for compound **23** (Scheme 2, Entry 8), the range of ratios observed between the four products (Scheme 3b) clearly identifies pH as a worthy variable for investigation should selectivity for a certain target be sought in similar circumstances.[36f] Finally, at the dimer level, varying patterns of protection on the phenols was shown to influence the oxidative dimerization event and provide access to other natural products cores such as **33** and **34**, partially protected forms of ampelopsin F and tetraarylfuran tricuspidatol A, albeit in modest yields (Scheme 3c).[38]

As to biomimetic endeavors towards higher levels in the oligomeric family there are only two reports, both of which detail the generation of trimers (and one tetramer) using oxidative conditions. The results of these experiments are shown in Scheme 4. The first report was actually not an effort in total synthesis but rather an attempt to support the biosynthetic hypothesis that davidiol A (**35**) is the result of an oxidative coupling between resveratrol (**1**) and ε-viniferin (**21**).[39] The authors exposed a mixture of these two natural products, ε-viniferin being in enantiopure form, to horseradish peroxidase and H_2O_2, and obtained davidiol A (**35**) in 1.1% yield along with the tetrameric hopeaphenol (**10**) in 1.5% yield with two other resveratrol dimers. It is worthy of note that the trimer and the tetramer are isolated as single diasteriomers. Given that exposure of resveratrol alone to horseradish peroxidase delivers exclusively racemic material,[36f] the stereoselectivity of this reaction may be confidently attributed to substrate control. This finding is in concert with the notion that a select few dimeric frameworks, such as ε-viniferin, could be biosynthesized as single enantiomers, after which further transformations

occur in a less controlled fashion without enzymatic assistance while maintaining stereochemical purity in the final adducts.

Scheme 4. a) Biomimetic Synthesis of Davidiol A. b) Biomimetic Synthesis of Laetevirenola B-D and Parthenocissin B



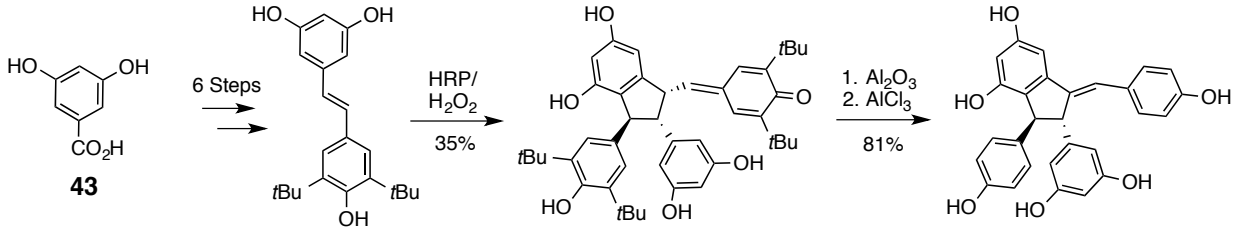
Lastly, in 2008, a study was published detailing the construction of laetevirenols C-E and parthenocissin B (**37**, **38**, **40**, and **41**) via the biomimetic coupling of resveratrol with quadrangularin A (**36**) or parthenocissin A (**39**) (Scheme 4b).[40] By treating a 2:1 mixture of quadrangularin A (**36**) and resveratrol (**1**) with horseradish peroxidase and H_2O_2, laetevirenols C and D (**37** and **38**) were produced and isolated in 14% yield each. An analogous procedure was employed using parthenocissin A (**39**) and resveratrol to obtain laetevirenol E and parthenocissin B (**40** and **41**) each in 15% yield. Given the multiple plausible pathways in which radicals generated from these species could have reacted, the yields are quite impressive. An explanation

is found in the fact that, much like the dimerization that produces δ-viniferin from two resveratrol radicals (see Scheme 2), these products are also the result of two radicals generated on the *para*-substituted phenol rings combining and their relative stability, when compared to other possible radicals, likely accounts for the observed selectivity. Additionally, the authors describe the photo-induced cyclization of parthenocissin B (**41**) to form laetevirenol B (**42**) in 21% yield and note the potential of this transformation to be biomimetic of biosynthetic relevance.

1.6.2 Hou Synthesis of Quadrangularin A

The transition into rationally designed synthetic approaches to resveratrol oligomers is smoothly ushered in by the semi-biomimetic synthesis of quadrangularin A (**36**) reported by the Hou group in 2006 (Scheme 5).[41] Key to this route is the dimerization of resveratrol derivative **44,** wherein the *para*-substituted phenol moiety is flanked by two *tert*-butyl groups. Given the

Scheme 5. Total Synthesis of Quadrangularin A By Li and Hou.



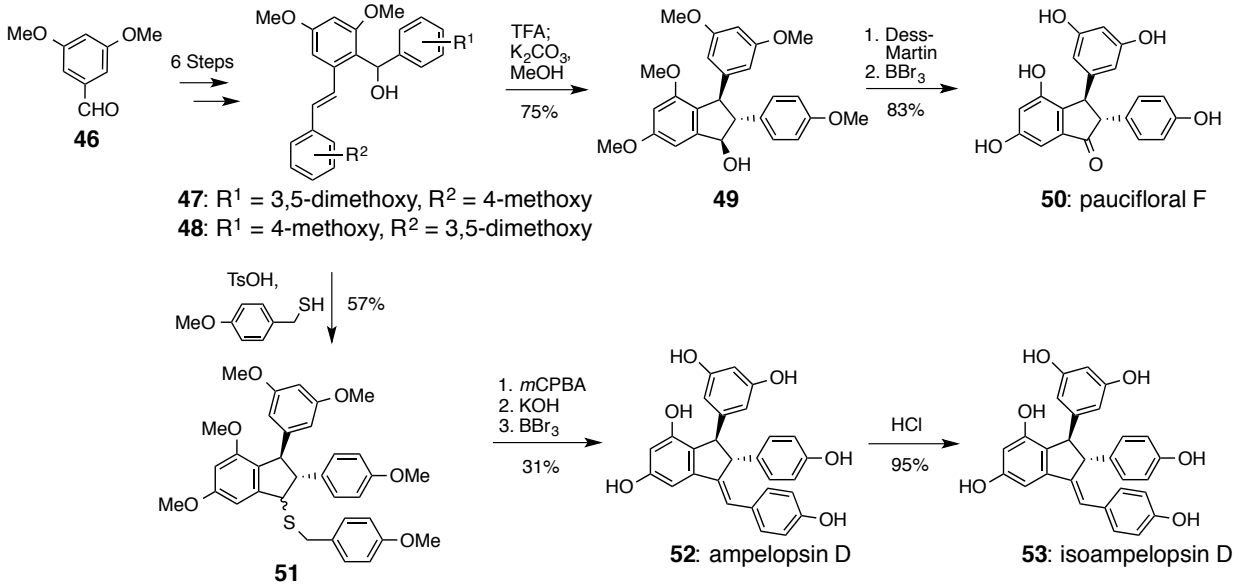
previously shown propensity of resveratrol to dimerize to δ-viniferin (**21**, Scheme 2) by coupling at the *para*-substituted ring, this *ortho*-blocking is a clever strategy to prevent such a pathway. The coupling precursor was assembled through standard chemistry and then submitted to the action of horseradish peroxidase and H_2O_2 in acetone to give the coupled product **45** in 35% yield with no recovery of other dimeric products (although trace amounts of resveratrol trimers

are mentioned). Interestingly, the isolated dimer from this reaction retains a *para*-quinone methide which the authors are able to characterize fully. Aromaticity is restored upon simple exposure to alumina, and finally the natural product unveiled following Lewis acid-mediated removal of the *tert*-butyl groups. These operations proceeded collectively in 81% yield. This work represents not only one of the first resveratrol oligomer syntheses to employ primarily standard synthetic chemistry, but also a well conceived tactic to overcome the established propensity of such oxidative conditions to induce coupling at the *para*-substituted phenol.

1.6.3 General Approach to Resveratrol Dimer Synthesis

In a 2007 communication and 2009 full article follow-up, the Snyder group described the first, and to date only, general approach towards accessing many diverse frameworks within the resveratrol class, only a selection of which will be shown here.[42] This strategy hinges on the identification of a common, non-obvious intermediate in the general form of compound **47**/**48** (Scheme 6) where the oxygen substitution pattern varies depending on the desired final target.

Scheme 6. General Approach to Resveratrol Dimers by Snyder *et al.*

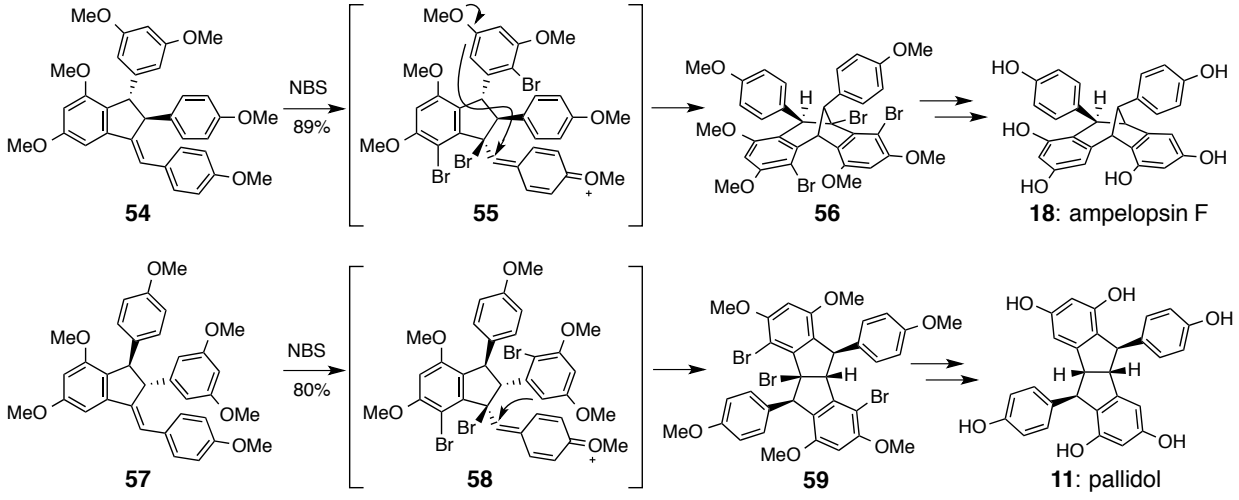


The value of this intermediate lies not only in its ability to access numerous frameworks in a rapid and selective fashion, but also in that fact that it is produced on multidecagram scale without the need for chromatography from commercially available **46**.

As outlined in above in Scheme 6, simple treatment of **47** with an acid delivers an indane core with a cation capable of interception by various nucleophiles. Trapping of that cation with trifluoroacetate ion and ester hydrolysis gives **49**, which in turn delivers paucifloral F (**50**) smoothly after oxidation and methyl ether cleavage. Cation interception with *p*-methoxy-α-toluenethiol, on the other hand, produces tetraryl intermediate **51**. Oxidation to the sulfone followed by a Ramberg-Bäcklund reaction and deprotection gives ampelopsin D (**52**) and isoampelopsin D (**53**) after olefin isomerization, both of which can be deprotected using BBr_3. Applying the very same strategy while exchanging the aromatic rings as in compound **48** delivers quadrangularin A (**36**, not shown here).

Pushing forward with permethylated ampelopsin D and quadrangularin A (**54** and **57** respectively, Scheme 7), it was found that exposure to NBS as an electrophilic bromine source

Scheme 7. Total Synthesis of Ampelopsin F and Pallidol by Snyder *et al*.



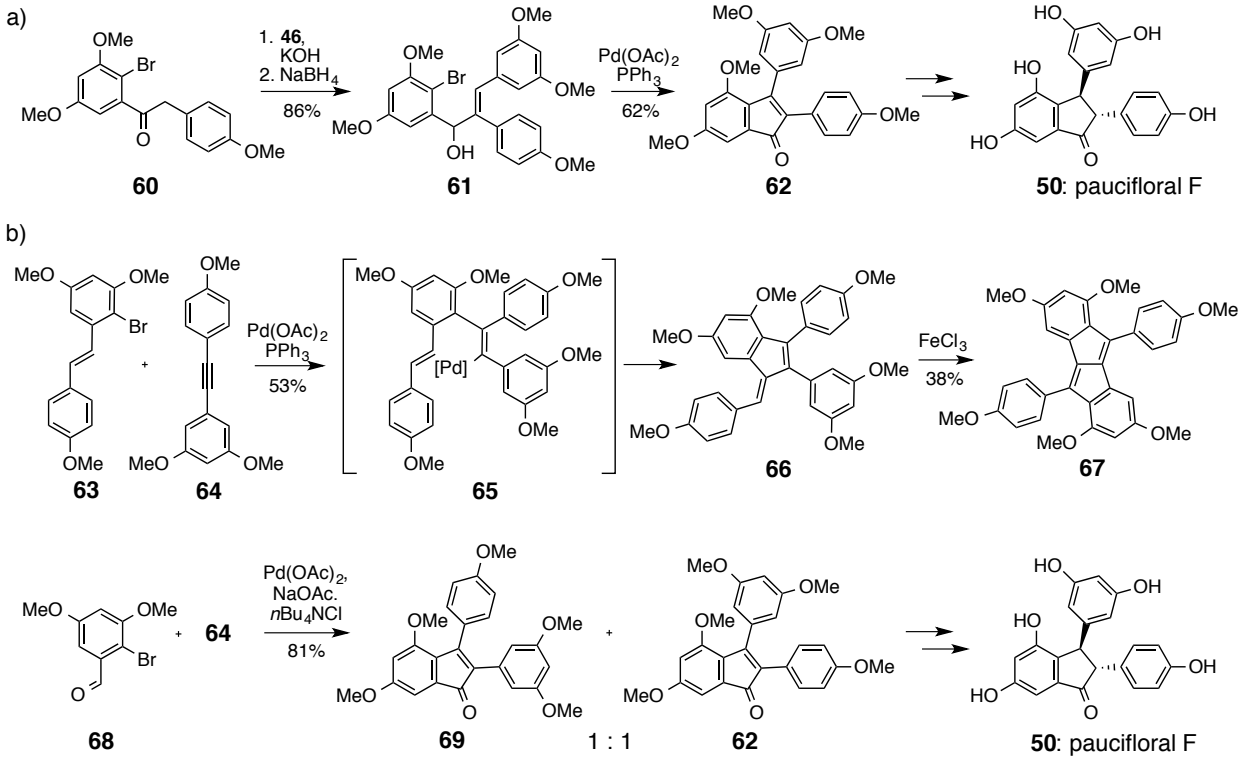
invoked the transformation of each substrate into its own unique, bicyclic core. From the

standpoint of atom economy, simple protonation of **54** and **57** on their olefins would be ideal, but such attempts merely isomerized the double bond into the five membered ring. Generation of a bromonium ion on the lone olefin of each substrate, however, induced the desired cyclization events and, critically, the reversible nature of electrophilic bromination allowed for addition onto the more hindered face (see compound **55**) of the double bond which was necessary to form the [3.2.1] bicycle of **56**. In the event, the two doubly oxygenated rings of both **54** and **57** proved to be more reactive towards NBS. Nonetheless, employment of 3.0 equivalents of NBS in each case delivered the desired bicyclic compounds **58** and **59**, after which reductive bromine removal followed by global deprotection produced the natural products pallidol (**11**) and ampelopsin F (**18**) in good yield.

1.6.4 Palladium Enabled Resveratrol Oligomer Synthesis

In an entirely unique approach, the She/Pan group in 2006[43] and the Sarpong group in 2009[44] published the use of palladium chemistry to generate a number of natural product-like frameworks as well as paucifloral F (**50**) itself. Shown in Scheme 8a, ketone **60** was transformed into allylic alcohol **61** through aldol condensation and subsequent ketone reduction. This intermediate smoothly underwent a Heck cyclization and concomitant oxidation using $Pd(OAc)_2$ to give core structure **62** in 62%, which could then be converted to the final product in three steps. In the Sarpong strategy, an equivalent of protected, brominated resveratrol (**63**) was exposed to $Pd(OAc)_2$ and, following oxidative addition to the C-Br bond, added across the alkyne of compound **64** in a regioselective manner. This compound then underwent *5-exo-trig* cyclization (via putative intermediate **65**) to ultimately deliver the quadrangularin A/parthenicissin A core (**66**). This cascade was then followed by an oxidative cyclization to

Scheme 8. Palladium Based Approaches. a) Gong/Fu Group. b) Sarpong Group

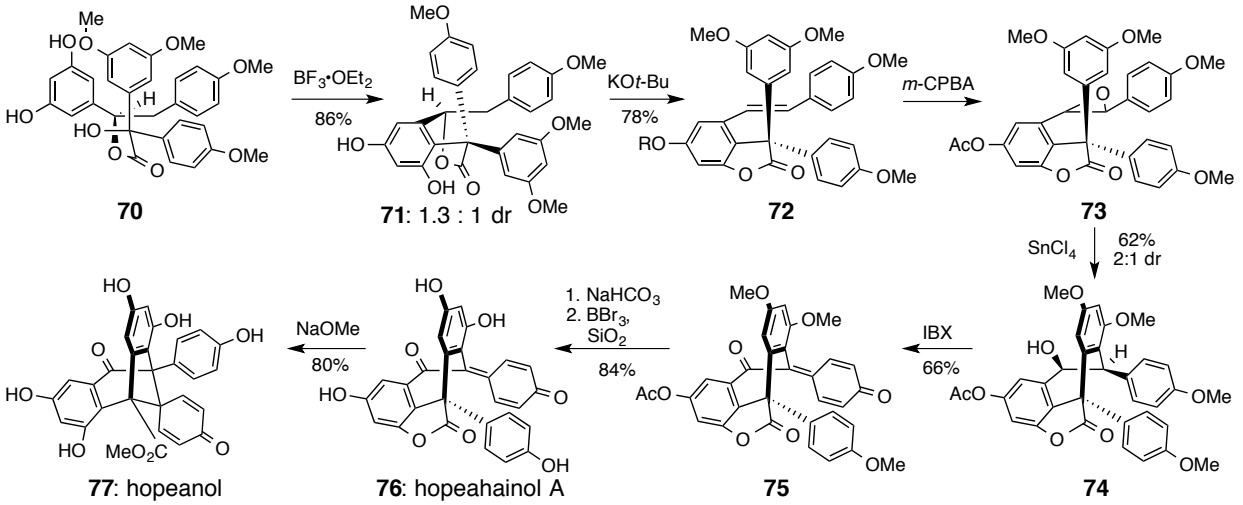


deliver an oxidized pallidol core (**67**). Later in the same year, the Sarpong group applied this strategy in the context of starting bromide **68** and accomplished an analogous cascade in 81% yield, albeit as a 1:1 mixture of regioisomers (**69** and **62**). The issue of regioselectivity is postulated to be the result of fast cyclization of the carbo-palladate intermediate in the case of bromide **68**, whereas the same mechanistic step in the previous substrate (**65**) may be under thermodynamic control. Nonetheless, the so-obtained indenone is brought to paucifloral F (**50**) using the standard transformations employed by the She/Pan group.

1.6.5 Total Synthesis of Hopeahainol A and Hopeanol

In 2009 and 2012, the Nicolaou and Snyder groups, respectively, published unique strategies towards the total syntheses of hopeahainol A (**76**) and hopeanol (**77**, Scheme 9) with the Nicolaou group adding a full article account of their synthetic efforts in 2010 that included an

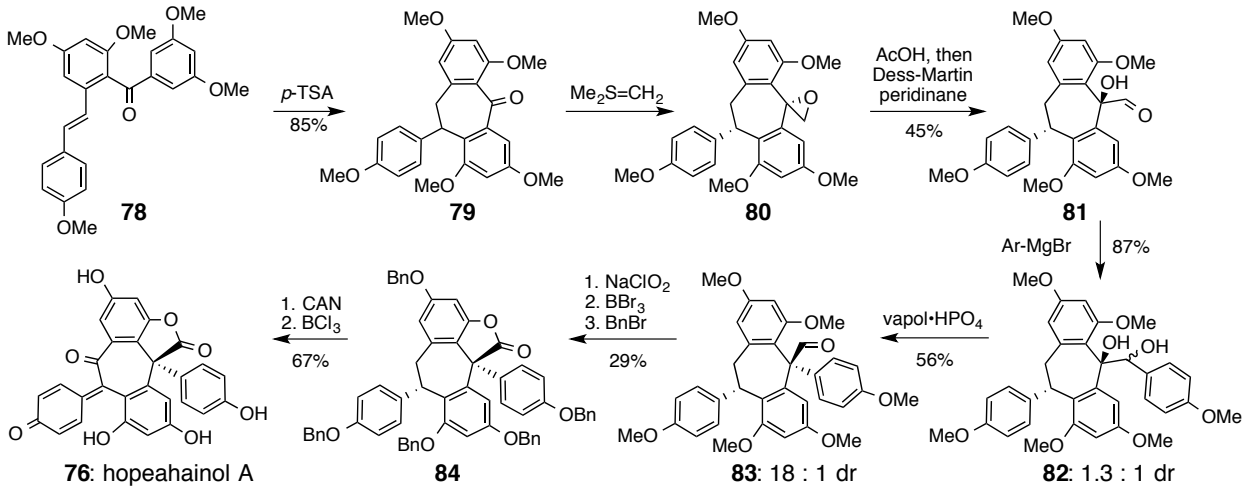
Scheme 9. Total Synthesis of Hopeahainol A and Hopeanol by Nicolaou *et al.*



asymmetric variant of their synthesis.[45,46] Particular interest was found in these two targets as hopeahainol A was reported by the isolation chemists to possess acetylcholinesterase activity, while hopeanol showed promise in cytotoxicity assays. The Nicolaou approach is summarized in Scheme 9 beginning with enantioenriched alcohol **70**, whose chirality was obtained via a CBS reduction earlier in the sequence (96% *ee*). **70** was treated with a Lewis acid to initiate a Friedel-Crafts cyclization that produced **71** in a 1.3 : 1 dr about the newly formed stereocenter favoring the desired outcome. Elimination of the carboxylate followed by lactonization on the adjacent phenol set up the substrate for the key epoxide induced cascade. In the event, treatment of **73** with *m*-CPBA followed by regioselective epoxide opening and Friedel-Crafts closure delivered seven membered ring **73** in 62% yield, favoring the desired diastereomer by a 2:1 margin. Finally, IBX oxidation produced *p*-quinone methide **74** and deprotection delivered hopeahainol A (**76**) with a smooth conversion to hopeanol (**77**) using basic methanol. Not only does this work exhibit the elegant use of conformational analysis and Friedel-Crafts chemistry, it represents the inaugural foray into asymmetric resveratrol oligomer synthesis.

The approach taken by Snyder *et al*. hinged on their biosynthetic hypothesis that the unique quaternary center of these natural products may arise from a pinacol rearrangement.

Scheme 10. Total Synthesis of Hopeahainol A and Hopeanol by Snyder *et al.*

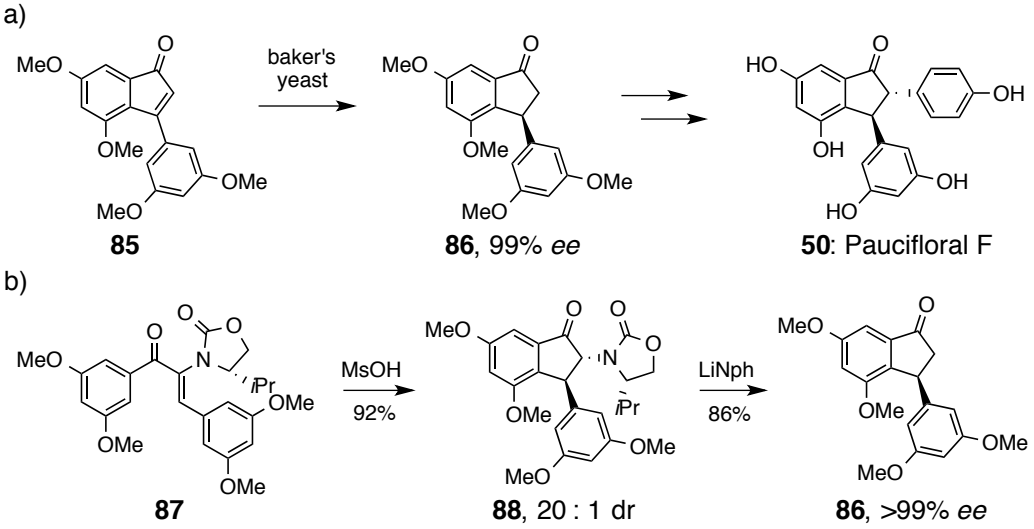


Illustrated in Scheme 10, seven membered ring ketone **79** is generated from intermediate **78**, the same common intermediate used in their previous work towards other dimeric natural products, (see Scheme 6, 7) and epoxidized under Corey-Chaykovsky conditions to give epoxide **80** as a single diastereomer. In a novel transformation, treatment of this epoxide with AcOH followed by Dess-Martin periodinane delivered the needed α-hydroxy aldehyde **81**, to which a fourth aryl ring was added as a Grignard reagent. An exhaustive screening of acid sources revealed that the specialized chiral phosphoric acid, vapol•HPO_4, could accomplish the desired pinacol rearrangement of **82** in 56% yield and in an impressive >18:1 dr about the newly formed quaternary center within product **83**. Interestingly, each antipode of vapol•HPO_4 produced the same dr, whereas a racemic mixture of this acid gave only 13.6:1 dr. Formation of the lactone proceeded without incident, after which reprotection with BnBr followed by treatment with CAN installed a benzylic ketone and quinone methide. BCl_3 deprotection gave the natural product hopeahainol A (**76**) and the transformation to hopeanol (**77**) was then re-confirmed using basic MeOH.

1.6.6 Asymmetric Synthesis of Paucifloral F

Apart from the above described asymmetric synthesis by Nicolaou, only two other reports of asymmetric resveratrol oligomer synthesis have been published. Both access paucifloral F and only the key steps of enantioinduction are shown below (Scheme 11). In 2011,

Scheme 11. Asymmetric Synthesis of Paucifloral F By a) Heo *et al.* b) Flynn *et al.*

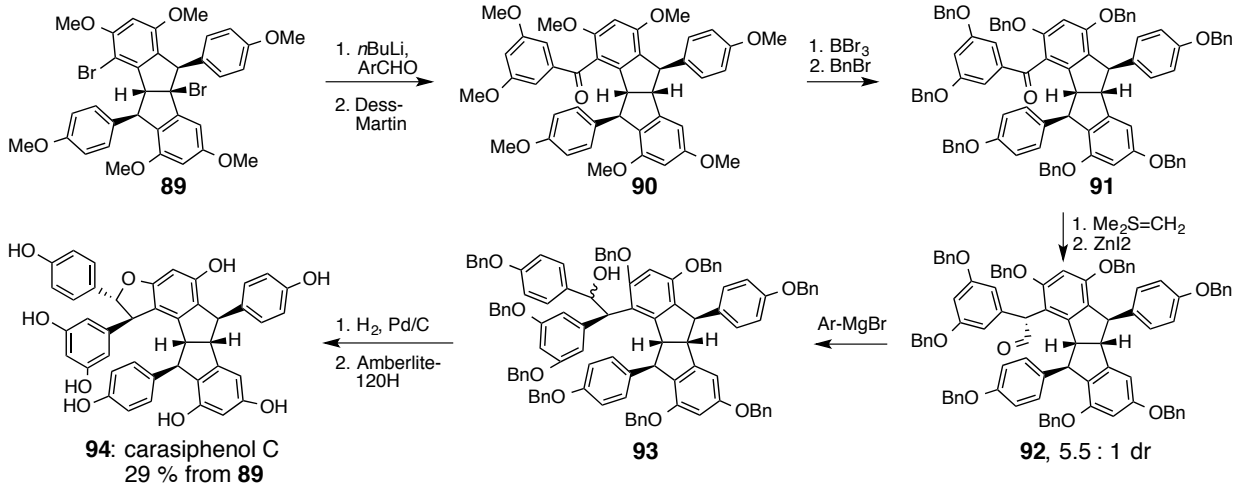


the Heo group accessed indenone intermediate **85** and accomplished a very successful asymmetric reduction of its olefin using baker's yeast to give **86**; subsequent α-arylation and deprotection produce the target molecule (**50**).[47] Two years later, the Flynn group intercepted the Hao route at intermediate **86** through what they refer to as "torquoselective Nazarov cyclization." In this step, enone **87** was treated with acid to induce the Nazarov cyclization, with reductive removal of the oxazolidinone auxillary of **88** completing the formal synthesis with >99% *ee*.[48] While a select few other oligomeric resveratrol-based products have been synthesized, what has been presented represents the primary contributions to the field at the dimer level.[49]

1.6.7 Total Synthesis of Resveratrol Trimers and Tetramers

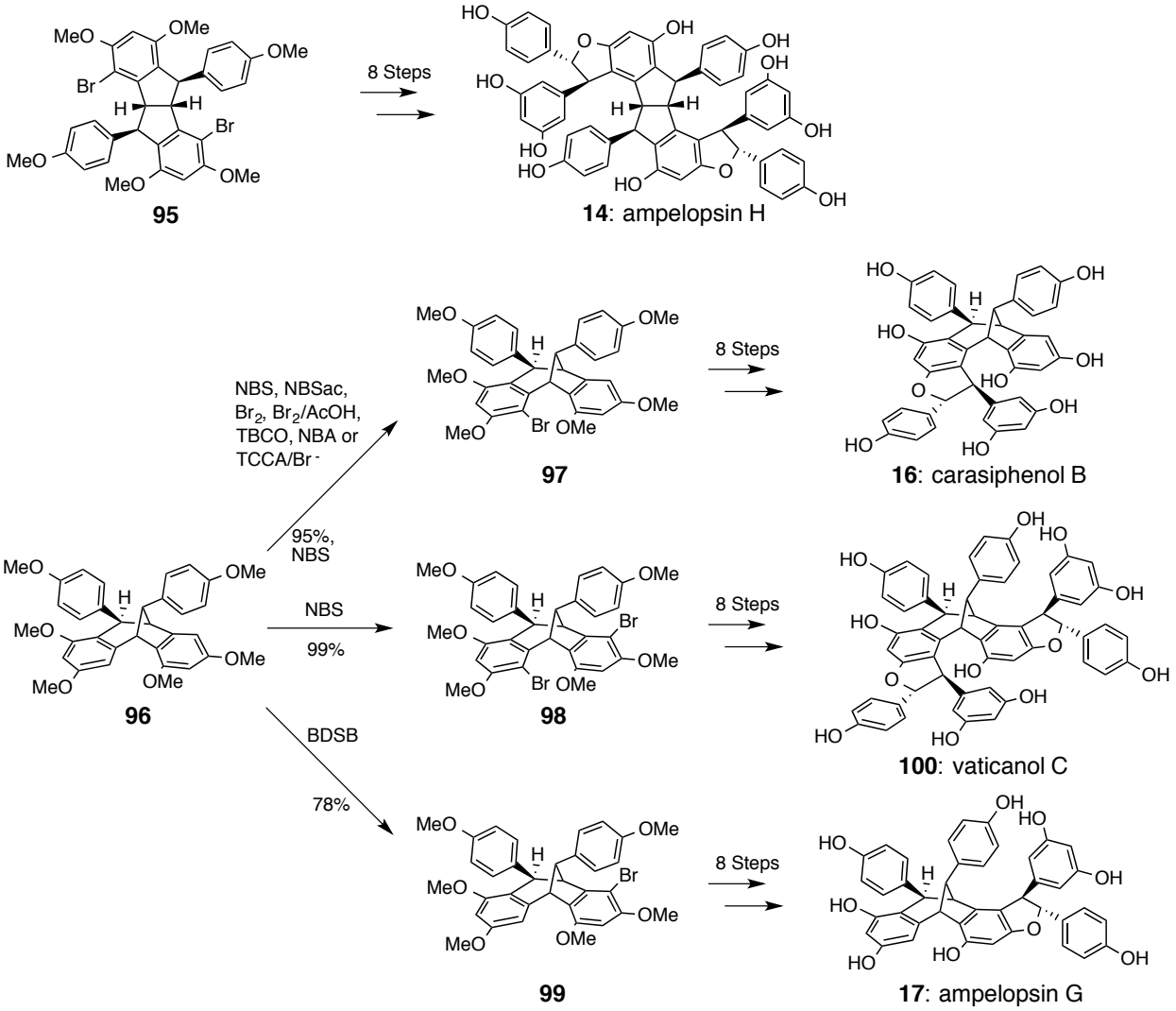
Up to this point, only synthetic efforts directed towards resveratrol-based dimers have been discussed. In fact, only one report of the total synthesis of higher order oligomers was published by Snyder *et al.* in 2011, where they describe the construction of three trimers and two tetramers.[50] This work exhibits the power to add resveratrol units, either 1 or 2 at a time, to existing dimeric frameworks and ultimately install the dihydrobenzofuran moiety ubiquitous to the resveratrol class. The fullness of this approach is shown in Scheme 12 through transformation of protected, brominated pallidol (**89**) into carasiphenol C (**94**). As shown, aryl lithium addition followed by Dess-Martin oxidation yielded ketone **90**. A protecting group

Scheme 12. Total Synthesis of Carasiphenol C by Snyder *et al.*



exchange then gave perbenzylated material **91**, a compound which then was extended to aldehyde **92** via a Corey-Chaykovsky epoxidation and subsequent Meinwald rearrangement. Finally, Grignard addition followed by global deprotection and acid treatment closed the dihydrobenzofuran to give carasiphenol C (**94**) in a yield of 29% over the eight step sequence. Notably, this route was accomplished on such a scale as to produce >50 mg of the final product in a single campaign. By applying the same sequence from aryl bromides (**95**, **97**-**99**), this team was able to achieve total syntheses of ampelopsin H (**14**), carasiphenol B (**16**),

Scheme 13. Total Syntheses of Ampelopsin H, Carasiphenol B, Vaticanol C, Ampelopsin G



vaticanol C (**100**), and ampelopsin G (**17**) as well as shown in Scheme 13. Not only does this work show the general applicability of their strategy for dihydrobenzofuran synthesis, it also offers a key contribution in the form of BDSB ($Et_2SBr•SbBrCl_5$), a brominating reagent developed by the Snyder group,[51] as a method for achieving uniquely site-selective functionalization when conventional reagents were uniformly unsuccessful.

1.7 Conclusion

This chapter has sought to provide a thorough overview of the resveratrol family of natural products: their history, biosynthesis, biological activity, and previous synthetic work. Since the isolation of resveratrol in 1939, hundreds of resveratrol-based natural products have been identified and characterized. The biological profile of resveratrol itself has garnered immense interest from the scientific community and continues to drive research into its potential as an anti-aging therapy as well as a probe to understand more fully the complex pathways involved in age-related diseases. While some natural products have been accessed through direct, biomimetic dimerization of resveratrol, they are few in number and the selectivity of those reactions is often limited. As such, synthetic chemists have devoted much effort towards the construction of these higher-order oligomers and successfully accessed many of them in a controlled fashion. It is important to note that much of the work to be presented in Chapters 2 and 3 has been conducted, and/or completed, concurrently with the synthetic efforts described in this introductory chapter. A complete survey, however, of synthetic work on resveratrol-based oligomeric natural products was deemed appropriate regardless of the specific timeline since each approach has proven to be quite distinct.

While impressive progress has been made in this field, challenges remain. Of the many dimeric frameworks available through the above-described chemistry, there still exists certain unique architectures that are not accessible through the previously established methods, so they require novel solutions. Among them are the natural products heimiol A and hopeahainol D (**15** and **20**, Figure 4). These structures represent two of a very rare subset of natural products in this class that possess a non-phenolic oxygen as part of their core framework. The specific challenges associated with that novelty will be discussed in Chapter 2.

Moreover the synthesis of such structures as complex as ampelopsin H and vaticanol C (**14** and **100**, Scheme 13) is a monumental step in the field. There are, however, select trimeric frameworks that cannot be produced by the methods described in that publication. Specifically, they are not derived from the appendage of resveratrol units onto a dimeric architecture, but rather possess core structures wholly unique to the trimer level such as α-viniferin (**19**, Figure 4). Synthetic work towards this nine membered ring containing subclass will be described in Chapter 3.

Finally, while the common intermediate developed by the Snyder Group (Schemes 6 and 7) has been shown to access numerous resveratrol-based oligomers, there are some which, as of yet, have eluded its grasp. Additionally, no general solution to asymmetric resveratrol synthesis currently exists from this, or any other, starting material. The few efforts described above are successful only in accessing one or two natural products in enantioenriched form and the need for an approach capable of bringing asymmetry to many of these structures remains. It is in these avenues where we sought to further the progress of this exciting field and to which this thesis is devoted.

Section 1.8 References

1. M. Takaoka, *J. Chem. Soc. Japan* **1939**, *60*, 1090 - 1100.

2. H. K. Felter, J. U. Lloyd, *King's American Dispensatory.* **1898**, *Veratrum Album - White Hellebore.*

3. H. K. Felter, T*he Eclectic Materia Medica, Pharmacology and Therapeutics* **1922**, *Vertatrum Album.*

4. G. Hrazdina, G. F. Parsons, L. R. Mattick, *Am. J. Enol. Vitic.* **1985**, *35*, 220 - 227.

5. A. Schoppner, H. Kindl, *J. Biol. Chem.* **1984**, *259*, 6806 - 6811.

6. P. Langcake, R. J. Pryce, *Phytochemistry* **1977**, *16*, 1193 - 1196.

7. P. Langcake, C. A. Cornford, R. J. Pryce, *Phytochemistry* **1979**, *18*, 1025 - 1027.

8. F. Hanawa, S. Tahara, J. Mizutani, *Phytochemistry*, **1992**, *31*, 3005 - 3007.

9. M. K. Arora, R. N. Strange, *Plant Sci.* **1991**, *78*, 157 - 163.

10. L. L. Creasy, M. Coffee, *J. Am. Soc. Hortic. Sci.* **1988**, *113*, 230 - 234.

11. P. Jeandet, R. Bessis, M. Sbaghi, P. Meunier, *J. Phytopathol.* **1995**, *143*, 135 - 139.

12. G. J. Soleas, E. P. Diamandis, D. M. Goldberg, *Clin. Biochem.* **1997**, *30*, 91 - 113.

13. E. H. Siemann, L. L. Creasy, *Am. J. Enol. Vitic.* **1992**, *43*, 49 - 52.

14. D. M. Goldberg, S. E. Hahn, J. G. Parkes, *Clin. Chim. Acta.* **1995**, *237*, 155 - 187.

15. For Selected Reviews see: (a) P. Saiko, A. Szakmary, W. Yaeger, T. Szekeres, *Rev. Mutation Res.* **2007**, *658*, 68 - 94; (b) T. Walle, F. Hsieh, M. H. DeLegge, J. E. Oatis, U. K. Walle, *Drug, Metab. Dispos.* **2004**, *32*, 1377 - 1382; (c) M. Athar, J. H. Back, X. Tang, K. H. Kim, L. Kopelovich, D. R. Bickers, A. L. Kim, *Toxicol. Appl. Pharmacol.* **2007**, *224*, 274 - 278; (d) P. Kopp, *Eur. J. Endocrinol.* **1998**, *138*, 619 - 620.

16. (a) M. T. Huang, C. T. Ho, C. Y. Lee, Eds. *Phenolic compounds in food and their effect on health*, Vols 1 and 2. Washington, DC: American Chemical Society, 1992; (b) A. H. Ensminger, M. E. Ensminger, J. E. Konlande, J. R. K. Robson, *Food and nutrition encyclopedia*. 2nd Ed, Vol. 1, Boca Roton: CRC Press, 1994.

17. K. T. Horowitz, K. J. Bitterman, H. Y. Cohen, D. W. Lamming, S. Lavu, J. G. Wood, R. E. Zipkin, P. Chung, A. Kisielewski, L. L. Zhang, B. Scherer, D. A. Sinclair, *Nature* **2003**, *425*, 191 - 196.

18. (a) J. G. Wood, B. Rogina, S. Lavu, K. Howitz, S. L. Helfand, M. Tatar, D. Sinclair, *Nature* **2004**, *430*, 686 - 689; (b) J. Gruber, S. Y. Tang, B. Halliwell, *Ann. NY Acad. Sci.* **2007**, *1100*, 530 - 542.

19. D. R. Valenzano, E. Terzibasi, T. Genade, A. Cattaneo, L. Domenici, A. Cellerino, *Curr. Biol.* **2006**, *16*, 296 - 300.

20. (a) R. A. Miller, D. E. Harrison, C. M. Astle, J. A. Baur, A. R. Boyd, R. de Cabo, E. Fernandez, K. Flurkey, M. A. Javors, J. F. Nelson, C. J. Orihuela, S. Pletcher, Z. D. Sharp, D. Sinclair, J. W. Starnes, J. E. Wilkinson, N. L. Nadon, R. Strong, *J. Gerontol. A. Biol. Sci. Med. Sci.* **2011**, *66*, 191 - 201; (b) P. L. da Luz, L. Tanaka, P. C. Brum, P. M. Dourado, D. Favarato, J. E. Krieger, F. R. Laurindo, *Atherosclerosis* **2012**, *224*, 136 - 142.

21. J. A. Baur, K. J. Pearson, N. L. Price, H. A. Jamieson, C. Lerin, A. Kalra, V. V. Prabhu, J. S. Allard, G. Lopez-Lluch, K. Lewis, P. J. Pistell, S. Poosala, K. G. Becker, O. Boss, D. Gwinn, M. Wang, S. Ramaswamy, K. W. Fishbein, R. G. Spencer, E. G. Lakatta, D. Le Couteur, R. J. Shaw, P. Navas, P. Puigserver, D. K. Ingram, R. de Cabo, D. A. Sinclair, *Nature* **2006**, *444*, 337 - 342.

22. S. J. Lin, P. A. Defossez, L. Guarente, *Science* **2000**, *289*, 2126 - 2128.

23. D. B. Lombard, S. D. Pletcher, C. Canto, J. Auwerx, *Nature* **2011**, *477*, 410 - 411.

24. B. P. Hubbard, A. P. Gomes, H. Dai, J. Li, A. W. Case, T. Considine, T. V. Riera, J. E. Lee, S. Y. E, D. W. Lamming, B. L. Pentelute, E. R. Schuman, L. A. Stevens, A. J. Ling, S. M. Armour, S. Michan, H. Zhao, Y. Jiang, S. M. Sweitzer, C. A. Blum, J. S. Disch, P. Y. Ng, K. T. Howitz, A. P. Rolo, Y. Hamuro, J. Moss, R. B. Perni, J. L. Ellis, G. P. Vlasuk, D. A. Sinclair, *Science* **2013**, *339*, 1216 - 1219.

25. S.-J. Park, F. Ahmad, A. Philp, K. Baar, T. Williams, H. Luo, H. Ke, H. Rehmann, R. Taussig, A. L. Brown, M. K. Kim, M. A. Beaven, A. B. Burgin, V. Manganiello, J. H. Chung, *Cell* **2012**, *148*, 421 - 433.

26. T. Ito, T. Tanaka, K. Nakaya, M. Iinuma, Y. Takahashi, H. Naganawa, M. Ohyama, Y. Nakanishi, K. F. Bastow, K.-H. Lee, *Tetrahedron Lett.* **2001**, *42*, 5909 - 5912.

27. For a Review: R. H. Cichwicz, S. A. Kouzi, *Stud. Nat. Prod. Chem.* **2002**, *26*, 507 - 579.

28. (a) L. B. Davin, H.-B. Wang, A. L. Cowell, D. L. Bedger, D. M. Martin, S. Saranene, N. G. Lewis, *Science* **1997**, *275*, 362 - 366; (b) D. A. Gang, M. A. Costa, M. Fujita, A. T.

Dinkova-Kostova, H.-B. Wang, V. Burlat, W. Martin, S. Sarkanen, L. B. Davin, N. G. Lewis, *Chem. Biol.* **1999**, *6*, 143 - 151.

29. M. Takaoka, *Proceedings of the Imperial Academy* **1940**, *16*, 405 - 407.

30. As an example: J. McNulty, P. Das, *Eur. J. Org. Chem.* **2009**, 4031 - 4035.

31. As an example: M. Guiso, C. Marra, A. Farina, *Tetrahedron Lett.* **2002**, *43*, 597 - 598.

32. P. Coggon, N. F. Janes, F. E. King, T. J. King, R. J. Molyneux, J. W. W. Morgan, K. Sellars, *J. Chem. Soc.* **1965**, 406 - 409.

33. P. Langcake, R. J. Pryce, *Experientia* **1977**, *33*, 151 - 152.

34. P. Langcake, R. J. Pryce, *J. Chem. Soc., Chem. Comm.* **1977**, 208 - 210.

35. R. Pezet, C. Perret, J. B. Jean-Denis, R. Tabacchi, K. Katia, O. Viret, *J. Agric. Food Chem.* **2003**, *51*, 5488 - 5492.

36. (a) M. Wang, Y. Jin, C.-T. Ho, *J. Agric. Food Chem.* **1999**, *47*, 3974 - 3977; (b) S. Nicotra, M. R. Cramarossa, A. Mucci, U. M. Pagnoni, S. Riva, L. Forti, *Tetrahedron* **2004**, *60*, 595 - 600; (c) M. Sako, H. Hosokawa, T. Ito, M. Iinuma, *J. Org. Chem.* **2004**, *69*, 2598 - 2600; (d) L. M. Szewczuk, S. H. Lee, I. A. Blair, T. M. Penning, *J. Nat. Prod*. **2005**, *68*, 36 - 42; (e) Y. Takaya, K. Terashima, J. Ito, Y.-H. He, M. Tateoka, N. Yamaguchi, M. Niwa, *Tetrahedron* **2005**, *61*, 10285 - 10290; (f) C. Li, J. Lu, X. Xu, R. Hu, Y. Pan, *Green Chem.* **2012**, *14*, 3281 - 3284.

37. C.-S. Yao, M. Lin, Y.-H. Wang, *Chin. J. Chem.* **2004**, *22*, 1350 - 1355.

38. S. S. Velu, I. Buniyamin, L. K. Ching, F. Feroz, I. Noorbatcha, L. C. Gee, K. Awang, I. A. Wahab, J.-F. F. Weber, *Chem. Eur. J.* **2008**, *14*, 11376 - 11384.

39. Y.-H. He, Y. Takaya, K. Terashima, M. Niwa, *Heterocycles* **2006**, *68*, 93 - 100.

40. S. He, B. Wu, Y. Pan, L. Jiang, *J. Org. Chem.* **2008**, *73*, 5233 - 5241.

41. W. Li, H. Li, Y. Li, Z. Hou, *Angew. Chem. Int. Ed.* **2006**, *45*, 7609 - 7611.

42. (a) S. A. Snyder, A. L. Zografos, Y. Lin, *Angew. Chem. Int. Ed.* **2007**, *46*, 8186 - 8191; (b) S. A. Snyder, S. P. Breazzano, A. G. Ross, Y. Lin, A. L. Zografos, *J. Am. Chem. Soc.* **2009**, *131*, 1753 - 1765.

43. B. Chen, J.-P. Lu, X.-G. Xie, X.-G. She, X.-F. Pan, *Chin. J. Org. Chem.* **2006**, *26*, 1300 - 1302.

44. (a) J. L. Jeffrey, R. Sarpong, *Tetrahedron Lett.* **2009**, *50*, 1969 - 1972; (b) J. L. Jeffrey, R. Sarpong, *Org. Lett.* **2009**, *11*, 5450 - 5453.

45. (a) K. C. Nicolaou, R. T. Wu, Q. Kang, D. Y.-K. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 3340 - 3343; (b) K. C. Nicolaou, Q. Kang, R. T. Wu, C. S. Lim, D. Y.-K. Chen, *J. Am. Chem. Soc.* **2010**, *132*, 7540 - 7548.

46. S. A. Snyder, S. B. Thomas, A. C. Mayer, S. P. Breazzano, *Angew. Chem. Int. Ed.* **2012**, *51*, 4080 - 4084.

47. B. H. Lee, Y. L. Choi, S. Shin, J.-N. Heo, *J. Org. Chem.* **2011**, *76*, 6611 - 6618.

48. D. J. Kerr, M. Miletic, N. Manchala, J. M. White, B. L. Flynn, *Org. Lett.* **2013**, *15*, 4118 - 4121.

49. For syntheses of other resveratrol oligomers see: (a) L. Chiummiento, M. Funicello, M. T. Lopardo, P. Lupattelli, S. Chppin, F. Colobert, *Eur. J. Org. Chem.* **2012**, 188 - 192; (b) Y. L. Choi, B. T. Kim, J.-N. Heo, *J. Org. Chem.* **2012**, *77*, 8762 - 8767; (c) S. A. Snyder, Z. G. Brill, *Org. Lett.* **2011**, *13*, 5524 - 5527.

50. S. A. Snyder, A. Gollner, M. I. Chiriac, *Nature* **2011**, *474*, 461 - 466.

51. S. A. Snyder, D. S. Treitler, *Angew. Chem. Int. Ed.* **2009**, *48*, 7899-7903.

Chapter 2

Total Synthesis of Heimiol A and Hopeahainol D

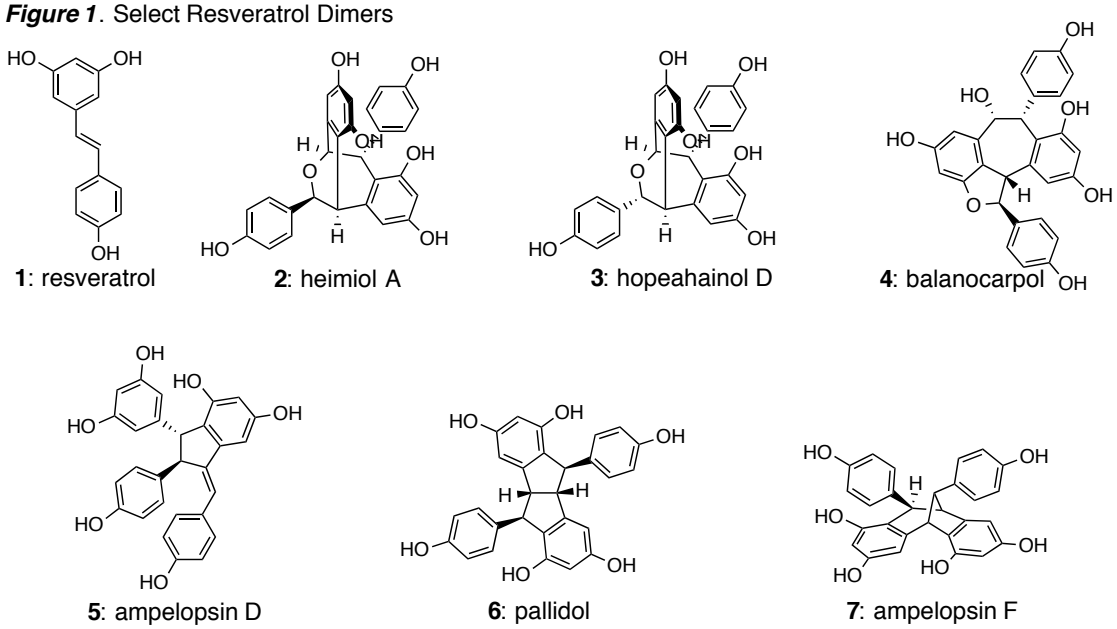
2.1 Isolation, Bioactivity, and Project Inspiration for Heimiol A and Hopeahainol D

Heimiol A (**2**, Figure 1) first came to light in a 2001 publication by Weber *et al.* that detailed its isolation from the heartwood extract of the plant *Neobalanocarpus heimii*.[1] In that report, the Weber group described their structure determination on the basis of mass spectrometry and 2D-NMR analysis. Since that initial isolation, heimiol A has been extracted from *Hopea dryobalanoides* (2005),[2] *Hopea mengarawan* (2006, 2008),[3] *Hopea hainanensis* (2009),[4] and *Hopea chinensis* (2012).[5] Among these reports, perhaps the most intriguing comes from its isolation out of the stem wood of *Hopea hainanensis* as hopeahainol D (**3**) was also characterized from the same extract as well as the already identified balanocarpal (**4**).[6] Hopeahainol D has only been isolated in one other instance from *Vatica mangachapai* in 2011.[7] It was in seeing these three compounds isolated together that our biosynthetic hypothesis toward these molecules, as well as part of our strategy for the construction of **2** and **3**, was inspired (*vide infra*).

As to the bioactivity of heimiol A and hopeahainol D, very little investigation has taken place thus far despite them being isolated on several occasions. Both compounds were tested for their radical-scavenging capacity, and each of them was found to have mild anti-oxidant activity.[4] Further testing revealed that heimiol A and hopeahainol D have neither acetylcholinesterase inhibitory properties[5,7] nor cytotoxicity, even after being used against several cancer cell lines.[2,3,8] While the argument may always be made, and it is a valid one, for the need of further testing because isolation efforts often produce quantities sufficient only for limited testing (such as the epothilones whose bioactivity was not elucidated until years after their initial isolation),[9] in this case it was in fact the structural features and synthetic challenge that principally drew our attention.

With the goal of the Snyder group being the ability to access all unique dimeric frameworks in the oligomeric resveratrol-based natural product family, heimiol A (**2**) and hopeahainol D (**3**) were attractive targets for the next phase of that endeavor and efforts towards their synthesis began in 2009. As discussed in the previous chapter, the Snyder group had successfully accessed a number of these resveratrol dimers in a selective manner from a common intermediate with compounds (**5**-**7**) shown in Figure 1 as representative examples.[10] While they

Figure 1. Select Resveratrol Dimers



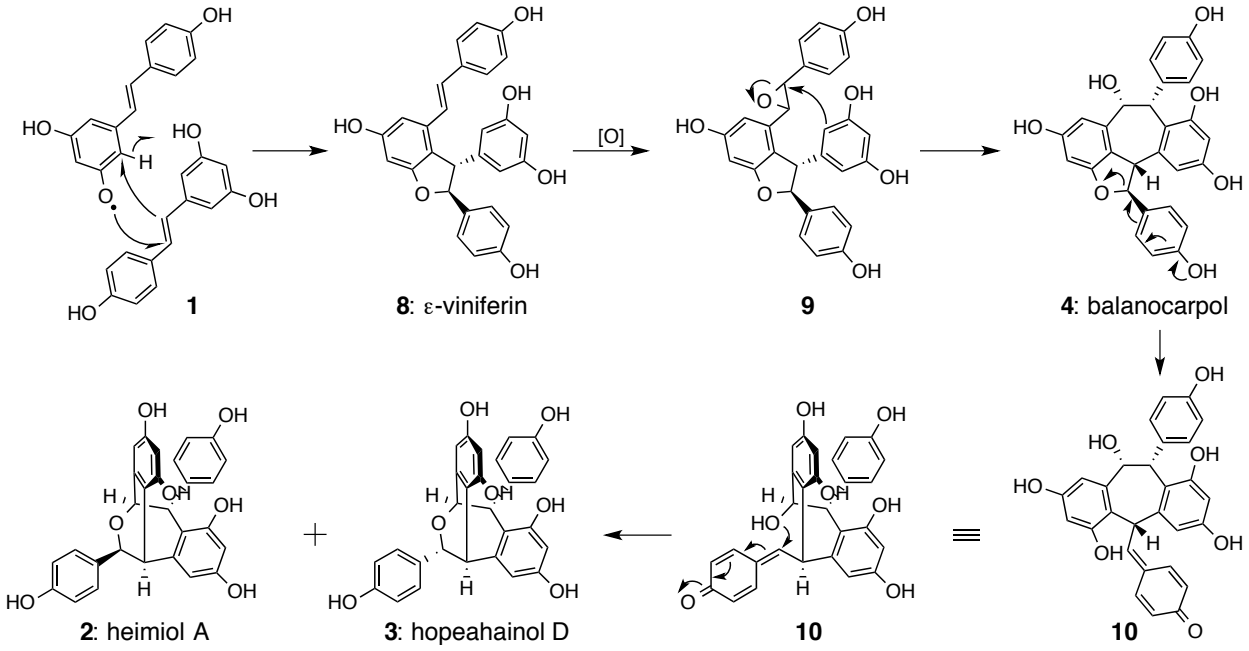
possess great diversity in their carbon frameworks, none of these targets deviate from the category of "pure dimer." In other words, there have been no additional structural features added apart from the atoms contained in two molecules of resveratrol (**1**). Heimiol and hopeahainol D, on the other hand, contain an additional oxygen atom, not as a ketone or pendant alcohol, as there are many examples of these, but rather ingrained in their core frameworks as a bridging ether. In fact, they are part of a very rare group of resveratrol-derived oligomers (we know of only three) possessing non-phenolic oxygen atom as part of their core framework. This step up the oxidation ladder, while simply stated, represents a non-trivial synthetic challenge, as will be

discussed. Our goal was to demonstrate that despite their unique features, these molecules could also be accessed from the common intermediate (**14**, see Scheme 2 below) developed by the Snyder group, thus expanding its scope to the realm of non-traditional dimeric natural products.

2.2 Proposed Biosynthesis of Heimiol A and Hopeahainol D

Despite the many isolations of heimiol A, and the two isolations of hopeahainol D, there is no proposed biosynthesis to account for the formation of either. The various reviews dedicated in part to the biosynthesis of resveratrol oligomers are silent on these two particular members of the class. We believe, however, that their co-isolation, as well as some *ab initio* calculations performed in our group, do hint at a reasonable biosynthetic hypothesis which is

Scheme 1. Proposed Biosynthesis of Heimiol A, Hopeahainol D



presented in Scheme 1. Let it be noted that this hypothesis has not been experimentally investigated in any capacity, but is in our opinion the most likely pathway by which the natural products are formed in Nature.

As shown in Chapter 1 (Section 1.5), oligomerization of resveratrol is widely accepted to begin with the oxidative union of two resveratrol units. The generation of ε-viniferin is reiterated here in order to show this biosynthetic proposal in its entirety (Scheme 1). Following dimerization of resveratrol (**1**) to ε-viniferin (**8**), we propose that enzymatic oxidation converts the olefin to an epoxide (**9**).[11] This epoxide opens at the indicated carbon due to greater stabilization of the positive charge, after which intramolecular Friedel-Crafts attack generates an all-carbon seven membered ring and the natural product balanocarpal (**4**). As noted earlier, balanocarpal was isolated with heimiol A and hopeahainol D which circumstantially supports our theory that their biosynthetic pathways might reasonably be related.

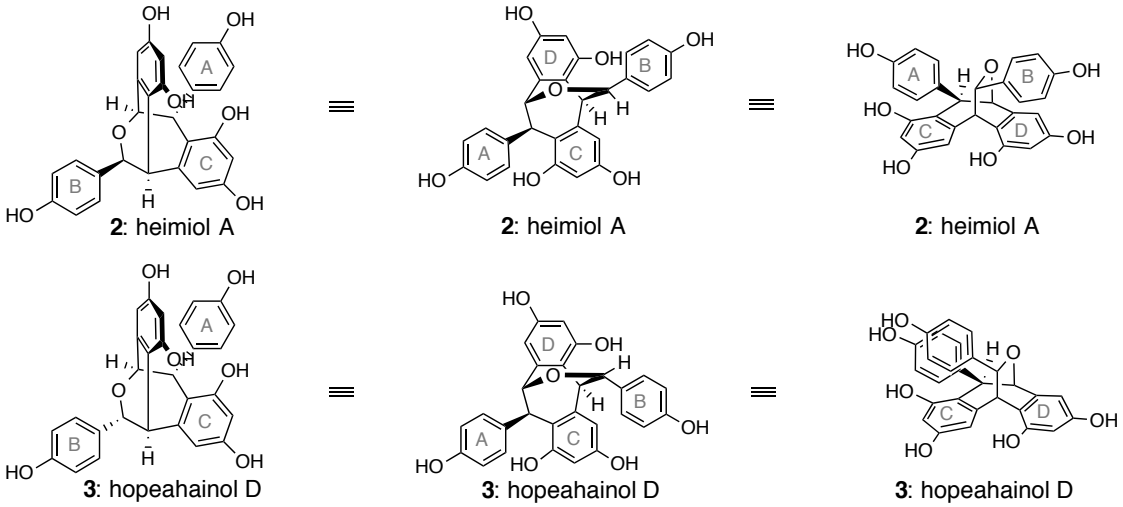
At this point in the proposal, it is appropriate to report that DFT calculations performed in our group revealed an interesting thermodynamic relationship among these three isomeric structures. If heimiol A (**2**) is defined to have a 0.0 kcal/mol ground state energy, then hopeahainol D (**3**) would be 1.8 kcal/mol higher, and balanocarpol even higher still in their ground state energies. Thus, if balanocarpal (**4**) was produced by the above-described pathway, then isomerization to the other two structures could, in theory, occur without the catalytic assistance of enzymes by simply walking down a "thermodynamic staircase" under acidic conditions assuming those conditions provided sufficient energy to overcome kinetic barriers. As graphically represented in Scheme 1, this process might occur by some acid-catalyzed opening of the dihydrobenzofuran of balanocarpal to generate stabilized benzylic cation **10**. At this point, two pathways are possible: 1) reclosing of the dihydrobenzofuran to reform balanocarpal (**4**) or 2) a conformational shift followed by transannular attack of the hydroxyl group onto the newly generated cation yielding either hopeahainol D (**3**) or heimiol A (**2**), dependant on the stereochemistry about the newly formed chiral center. This theory is plausible

given the thermodynamic benefit of such an isomerization. Furthermore, should hopeahainol D (**3**) be produced in this fashion, a similar event could be employed to transform it into heimiol A (**2**) through a similar cationic intermediate as **10**. Given that heimiol A is more widely and abundantly isolated than hopeahainol D, this hypothesis seems reasonable and we sought to use this knowledge of thermodynamic relationships to guide our synthetic strategy as outlined in the followed sections. As a final note, it suggests that these dimers are the result of rearrangement of other dimers, not *de novo* syntheses from resveratrol monomers.

2.3 Initial Approach Towards Heimiol A and Hopeahainol D

Given the well known influence of a molecular drawing on the chemists' approach for its synthesis, three renderings of heimiol A (**2**) and hopeahainol D (**3**) are set alongside one another

Figure 2. Multiple Perspective Drawings of Heimiol A and Hopeahainol D



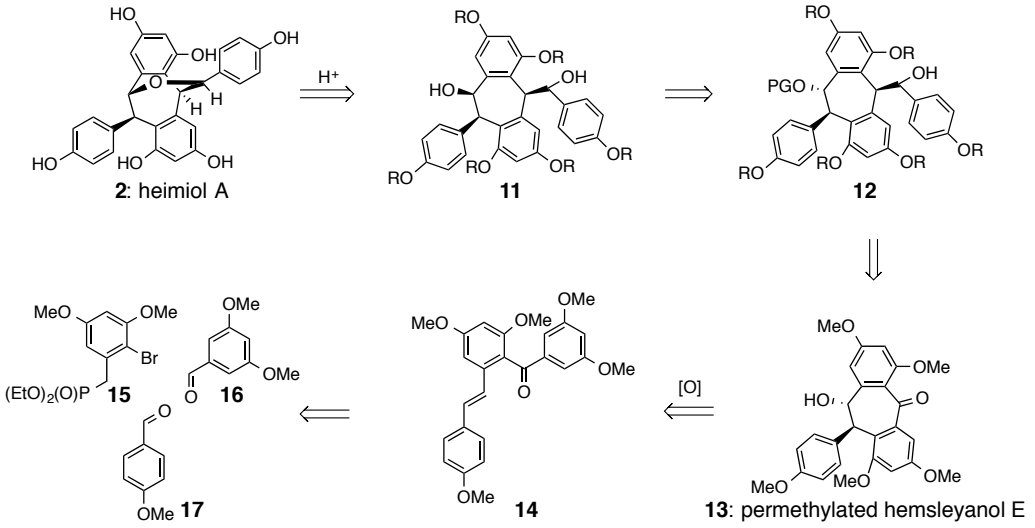
in Figure 2. While the drawing of the isolation chemists, the first set, portray these molecules in the most formidable light in terms of structural complexity, the second and third sets provide insight into some of the other key features and challenges present in the two frameworks. Specifically, in the second set of drawings, the all-carbon seven membered ring becomes more

clear as well as the relative stereochemistry of the three chiral centers it possesses. Indeed, all three centers possess groups that lay on the same face of the core 7-membered ring and thus any strategy for their installation must account for the need to achieve a less thermodynamically favored relationship among them. Additionally, the bridging ether is revealed as being bis-benzylic and thus likely to be very acid sensitive. Nearly every synthesis of resveratrol-based oligomers published up to this point has employed BBr_3 in the final step to remove methyl ether protecting groups (usually at 25 ^{o}C for many hours) and unveil the natural free phenols.[12] Thus, it is almost certain that the ether present in heimiol A and hopeahainol D will not withstand such harsh acidic conditions and an alternate protecting group strategy will need to be implemented. Finally, the third set of drawings makes more apparent the reason for a higher ground state energy in hopeahainol D. The placement of rings C and D on the same side of the ether bridge affords an unfavorable steric interaction and therefore, if we intend to synthesize both compounds, our approach must find a way to favor each epimer separately, likely needing to target hopeahainol D before heimiol A. With these challenges in mind, we set out to devise a retrosynthetic plan.

In an effort to continue showcasing the broad utility of the Snyder group "common intermediate" (**14**) for resveratrol oligomer synthesis, the first strategy for the construction of heimiol A and hopeahainol D begins there. As shown in retrosynthetic fashion (Scheme 2), the final bond formation was projected to be that of the ether bridge using benzylic alcohol ionization followed by transannular attack of the hydroxyl group from intermediate **11** in much the same manner as outlined in our biosynthetic hypothesis. For the reasons discussed in Section 2.2, we were confident that hydroxyl attack would be favored over that of the phenol, even if the phenol was unveiled prior to that point in the sequence. The stereochemistry of that hydroxyl

group would be established through oxidation of the epimeric alcohol **12** and subsequent kinetically driven reduction from the less hindered face; this event should force the resulting alcohol *syn* to its neighboring *para*-substituted ring as in **11**. Intermediate **12** would come from

Scheme 2. Initial Retrosynthetic Analysis Towards Heimiol A and Hopeahainol D

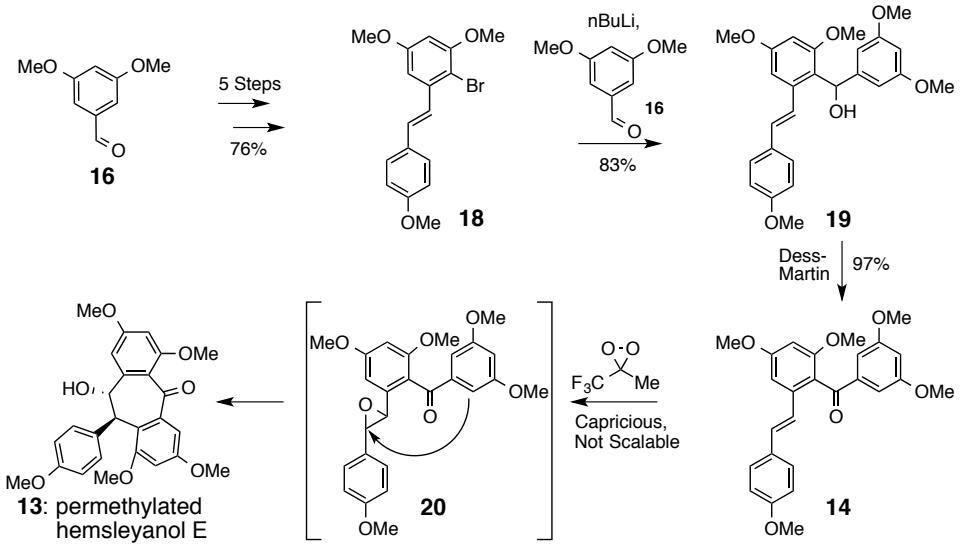


homologation of ketone **13** and Grignard addition into the resulting aldehyde. The keto-alcohol **13** had already been synthesized and published by the Snyder group in protected form and is in fact the protected natural product hemsleyanol E.[13] This compound was the result of epoxidation and cyclization from common intermediate **14**, material which itself could be built using standard chemistry from building blocks **15**-**17**.

In the forward direction (Scheme 3), commercially available aldehyde **16** was advanced to brominated resveratrol trimethyl ether **18** in five steps. The aryl lithium was then generated and added into aldehyde **16** to give triaryl alcohol **19.** Subsequent Dess-Martin oxidation[14] delivered ketone **14** in 81% overall yield. It is important to note at this stage that the aryl lithium addition was entirely unsuccessful if the protecting group on the neighboring phenol was anything other than a methyl ether. Presumably, the steric demands of this bond formation are prohibitively high if increased steric bulk is present in that neighboring position. It is at this

point that oxidative cyclization to give hydroxy-ketone **13** was sought. As reported by Snyder *et al.* in their 2009 full article,[10] no set of epoxidation conditions accomplished this transformation with the exception of *in situ* generated 1,1,1-triflurodimethyldioxirane,[15] even then, that process occurred in no better than 34% yield. In seeking to bring large quantities of material through this

Scheme 3. Initial Efforts Towards Intermediate **13**.

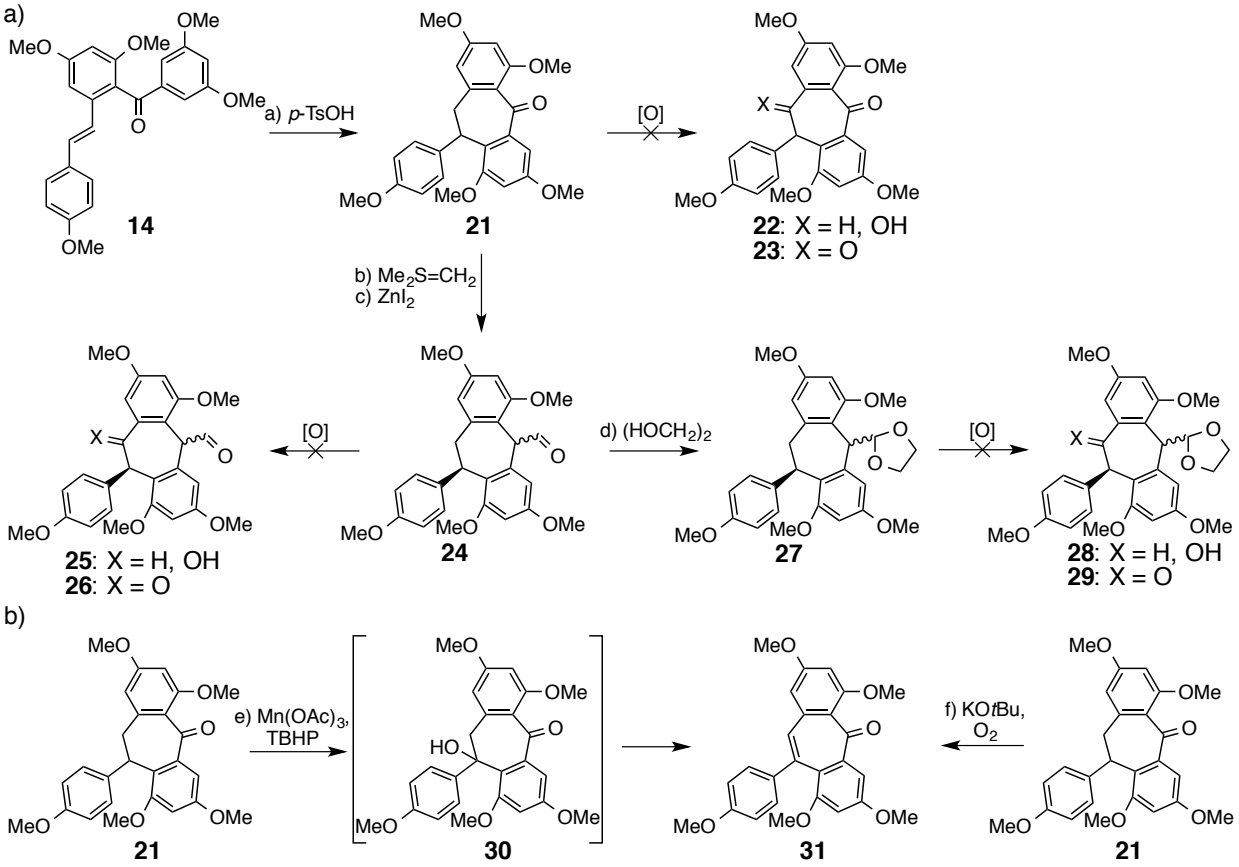


step for the synthesis of heimiol A and hopeahainol D, it was found that the reaction was, in fact, quite capricious, usually delivering low yields, and in some cases, no product; attempts to scale the reaction (the reported yield was on a 500 mg scale) only exacerbated these issues. When **13** is the final target, this procedure is suitable; it accomplishes the transformation and proves the principal of achieving this desired oxidative cyclization. However, as a launching point for further synthetic explorations, namely the targets upon which this chapter focuses, it was quickly realized that such a reaction was inadequate and alternate strategies were required.

Known cyclization of ketone **14** under acidic conditions to seven membered ring **21** worked well and reproducibly; as such, our first forays into alternate strategies consisted of benzylic oxidations of **21** hoping to install an oxygen atom (either as an alcohol or a ketone) on the already generated seven membered ring core (Scheme 4a). Despite being benzylic to a

highly electron-rich aromatic ring, no oxidation was observed using standard protocols.[16]

Scheme 4. a) Failed Benzylic Oxidation Attempts. b) Benzylic Oxidations Leading to Alkene **31.**



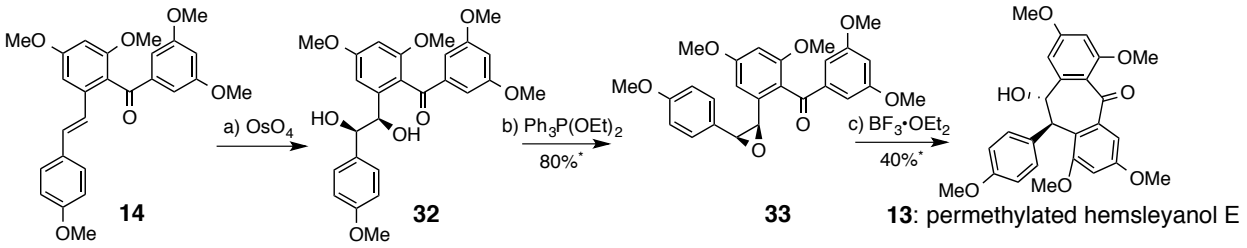
Reagents and Conditions: a) *p*-TsOH, tol., 80 ºC, 3 h, 85%; b) Me_3SI, *n*-BuLi, THF, 25 ºC, 12 h; c) ZnI_2, 14 h, 72% from **21**, 2.5:1 dr; d) $(HOCH_2)_2$, *p*-TsOH, tol., 110 ºC, 2 h, 81%; e) TBHP, $Mn(OAc)_3 \cdot 2H_2O$, 3Å M.S., EtOAc, 25 ºC, < 20%*; f) KO*t*Bu, O_2, THF, -78 ºC - 25 ºC, 12 h, ~30%*. * Yield estimated based on crude material recovery and/or crude ^1H NMR analysis.

Thinking that the ketone may be negatively affecting the desired pathway by pulling electron density away from the site of needed oxidation, that function was homologated to the corresponding aldehyde (**24**) but neither this intermediate, nor its dioxolane **27**, yielded to benzylic oxidation. The only somewhat successful reaction observed was the transformation to tentatively assigned tertiary alcohol **30** after treatment of **21** with $Mn(OAc)_3$ and TBHP (Scheme 4b).[17] The ^1H NMR spectral data was somewhat ambiguous, but upon standing, known compound **31** was obtained. Because this product likely arose from ionization of a hydroxyl group at either of the two pre-alkene carbons, and the other, desired hydroxylation site is known

(**13**, Scheme 3), we concluded that the product of $Mn(OAc)_3$ oxidation must have been **30**. The same alkene **31** was obtained again when attempting to exploit the ketone moiety of **21** by doing a "vinylogous" deprotonation through the π system of the aromatic ring, as shown, and trapping with oxygen.[18] As most benzylic oxidation attempts returned only unreacted starting material and the few conditions that accomplished some form of oxidation produced only alkene **31**, the decision was made to abandon this benzylic oxidation strategy and look for alternates.

Additional methods for achieving a more reliable synthesis of hydroxy-ketone **13**, or a closely related structure, were pursued next in search of identifying any key findings or insight for a more global approach. One such strategy was developed in reassessing the various epoxidation conditions already attempted on ketone **14** when it was noted that no two-step protocols had been attempted. Specifically, dihydroxylation of the alkene of **14** had been accomplished, but no efforts towards transforming that vicinal diol into an epoxide had been performed. Seeing as the direct epoxidation conditions were unsuccessful, potentially due to the electron rich aromatic rings, as opposed to the desired alkene, engaging the electrophilic oxygen, transformation of a diol into the epoxide presented itself as a viable alternative as no additional electrophilic species would be generated. Given the wealth of precedent for such a two-step transformation, this approach was pursued immediately. As shown in Scheme 5, the diol was

Scheme 5. Alternate, Successful Route to Intermediate **13**.



Reagents and Conditions: a) OsO_4, NMO, acetone/H_2O, 25 ºC, 5 h, 98%; b) $Ph_3P(OEt)_2$, tol., 70 ºC, 24 h, ~ 80%*; c) BF_3•OEt_2, CH_2Cl_2, -78 ºC - 25 ºC, ~ 40%*. * Yield estimated based on crude material recovery and/or crude ^1H NMR analysis.

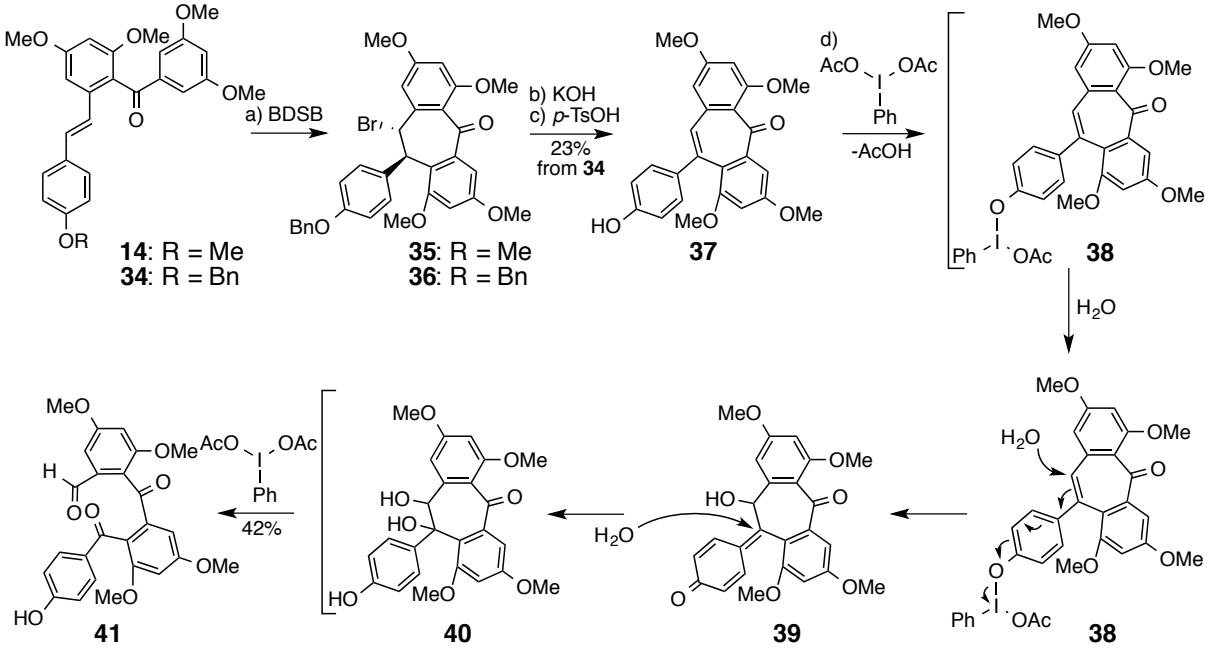
generated smoothly using OsO_4, although a yield for that exact step was not obtained due to product stability. [19] Pressing forward, intermediate **31** was then treated with diethoxytriphenylphosphorane [$Ph_3P(OEt)_2$], which delivered a compound we tentatively assigned as epoxide **32**.[20] It was found that this compound could be converted into protected hemsleyanol E (**13**) through simple Lewis acid treatment in an overall yield of approximately 32%. While less than ideal, this method represented a very attractive alternative to the dioxirane-induced cyclization discussed previously as it was highly reproducible.

Despite this approach representing the most promising thus far, it was not without limitations. First, this route took what was ideally a one step transformation and turned it into a three step alternative. And, although it was much more reliable, the yield was still relatively modest. Secondly, the dehydrating reagent [$Ph_3P(OEt)_2$] had to be prepared in refluxing toluene from Ph_3P and diethylperoxide $(EtO)_2$ which also had to be synthesized and purified via distillation prior to use. Given the propensity for peroxide containing compounds to explode,[21] purifying diethylperoxide required very careful protocols. Ignoring the limitations of this step itself, the subsequent proposed route from compound **13** contained costly oxidation state fluctuations (alcohol epimerization, Scheme 2) and questionable stereochemical issues (diastereoselectivity in the ketone elaboration from **13** to **12**). As discussed above, the bridging ether in the final compounds would likely be acid sensitive and unstable to methyl ether cleavage conditions. The route, however, provides no suitable intermediate for a switch to more labile protecting groups and methyl ethers were required for the successful synthesis of starting compound **14**. It is due to these limitations that additional strategies were simultaneously investigated. Of the many failed attempts to solve these collective issues, the one outcome which bestowed the greatest insight will be discussed in the next section.

2.4 Development of a Successful Oxidative Cyclization and Its Application to the Total Synthesis of Heimiol A and Hopeahainol D

Already published by the Snyder group was the generation of seven membered ring bromide **35** via bromonium-induced cyclization of the ketone **14** (Scheme 6). As shown, we embarked down a similar pathway using material with a single phenol orthogonally protected as a benzyl ether (**34** and **36**). The Snyder group had already established that any attempt to displace the newly installed bromide with an oxygen nucleophile through an S_N2 mechanism resulted either in no reaction, or 1,2-phenonium shift of the neighboring *para*-substituted ring to give a rearranged product. Instead, in this effort, we carried forward with an elimination of that bromide and removal of the benzyl protecting group to furnish monophenol **37**. It was at this

Scheme 6. Synthesis of Intermediate **37** and PIDA Enabled Oxidation Attempt.



Reagents and Conditions: a) BDSB, $MeNO_2$, -20 ºC, 1 h; b) KOH, 18-C-6, THF, 50 ºC, 12 h, 49% from **34**; c) *p*-TsOH, tol., 80 ºC, 2 h, 47%; d) $PhI(OAc)_2$, THF/H_2O, 25 ºC, 45 min, 42%.

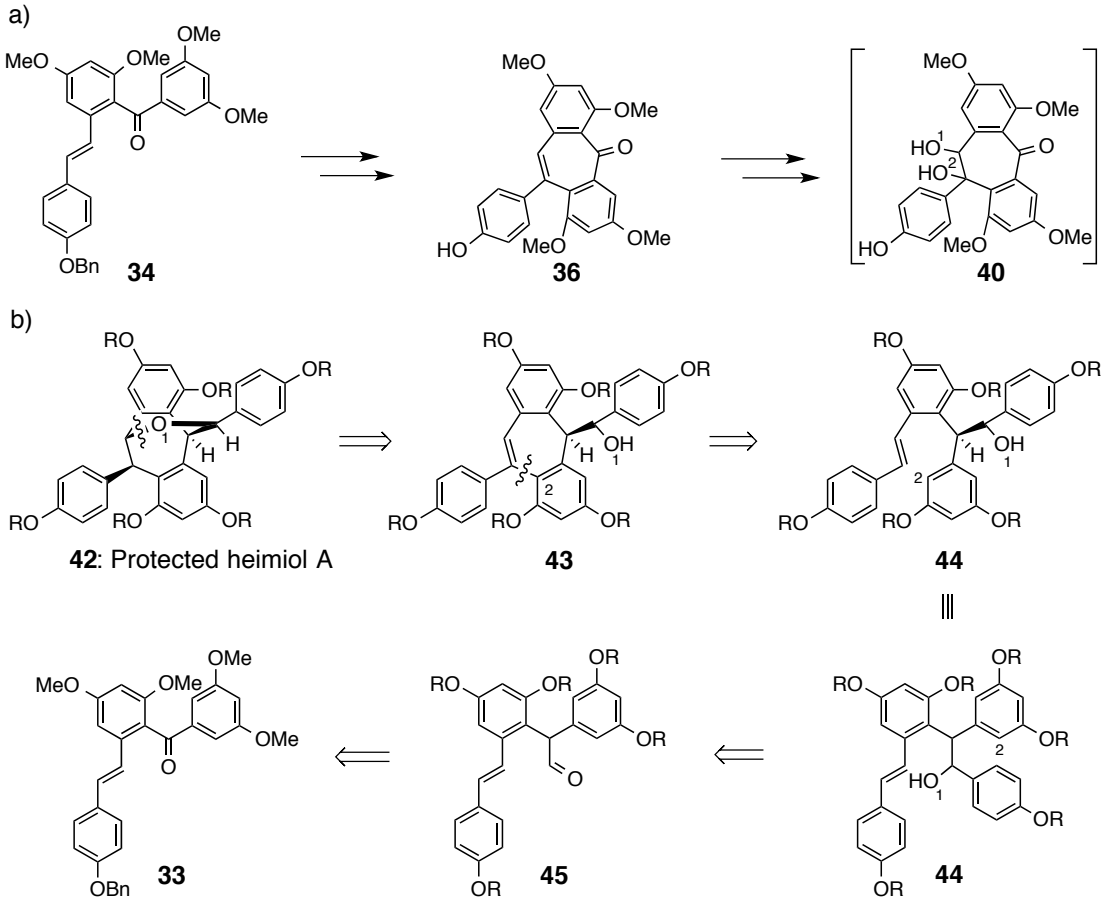
point that we attempted to install the desired alcohol through oxidation as directed by the single free phenol. Specifically, we hoped that treatment with $PhI(OAc)_2$, a reagent which has shown precedent for this type of reactivity,[22] would extract a pair of electrons through the phenol

(intermediate **38**) and induce attack by a nucleophilic oxygen species (water in this case) on the desired carbon. This event would generate *para*-quinone methide **39**, which would likely be attacked by a second equivalent of water to afford diol **40**. Although this second hydroxyl group was unwanted and would require subsequent reduction, the immediate goal was to probe the viability of this approach for incorporating the desired oxygen atom.

As shown in Scheme 6, it seems the material passed through our desired intermediate diol but then continued to react and was oxidatively cleaved to afford the only isolated product, diketo-aldehyde **41**. While this reaction, strictly speaking, was a failure in terms of the final product, the logic behind the design was sound. By oxidizing that alkene we were able to bring an oxygen nucleophile into the desired position. Using this finding, we believe the most straightforward solution to remedy the oxidative cleavage would be to use a nucleophile whose adduct would not cleave, perhaps an alcohol of some sort or an acetate group. However, with the concept of our oxidation proven, we then set out to uncover the best version of that idea and, in so doing, we devised the following approach.

For the purposes of visual clarity, the results of the above described experiment are summarized in Scheme 7a below with diol **40** shown in brackets because it was never isolated, being only an assumed intermediate. Additionally, the two hydroxyl groups are marked as 1 and 2 according to the order of their attack in the presumed mechanism for the reaction leading to its synthesis. Reassessing the structure of the natural product heimiol A (**42**, protected form), we see that the ether oxygen corresponds to alcohol group 1 in alleged intermediate **40**. The thought then came that instead of an external nucleophile attacking that position, perhaps an internal cyclization could occur instead; that event retrosynthetically leads back to intermediate **43**. While this process would, in theory, install the requisite ether bridge, there is still the issue of the

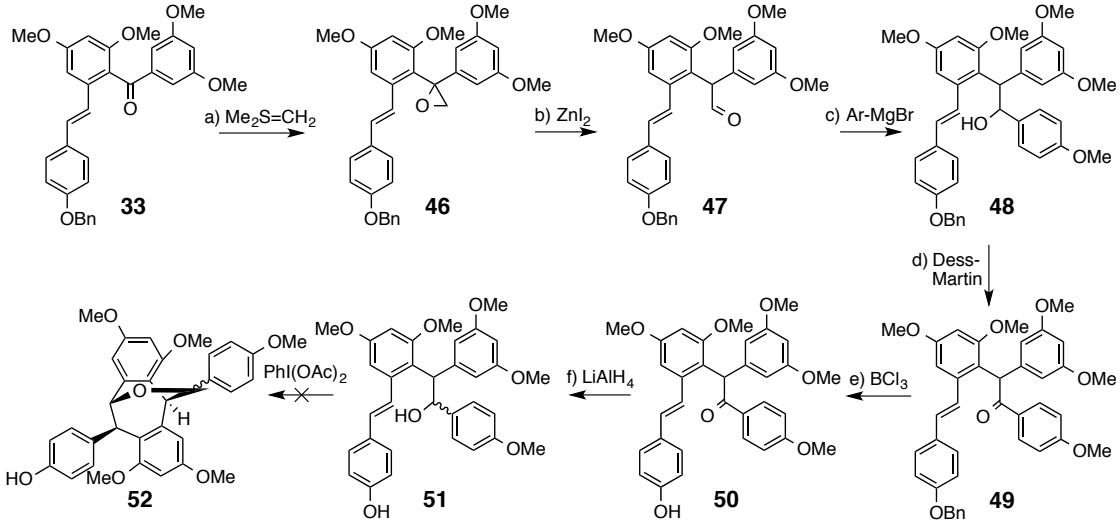
Scheme 7. a) Summary of $PhI(OAc)_2$ Oxidation. b) Newly Inspired Retrosynthetic Analysis.



second nucleophile addition to address (*i.e.* alcohol 2 of **40**). Were intermediate **43** to be submitted to the oxidation conditions, a second nucleophile would likely attack in the same manner and would then need to be replaced ultimately by a hydrogen atom. We noticed, however, that the indicated C-C bond also needed to be formed at some point. We asked then if the second nucleophile of this oxidative transformation could also be internal. Indeed, if the second nucleophilic attack were to come from the appropriate, electron-rich aromatic ring in the form of a Friedel-Crafts reaction, we would then be attempting an oxidative double cyclization of tetra-aryl alcohol **44**. Unwinding of this intermediate gives a clearer view which reveals its construction to most directly be accomplished by Grignard addition into aldehyde **45**, itself the product of homologation from common ketone intermediate **33**.

In the forward direction, common ketone **33** was prepared via the procedure outlined by Snyder *et al*.[10] with the only exception being the presence of the lone benzyl protecting group on the lower aromatic ring (Scheme 8). Corey-Chaykovsky epoxidation[23] followed by ZnI_2-mediated Meinwald rearrangement[24] resulted in the synthesis of aldehyde **47** in 80% yield over the two-step sequence. Interestingly, when the benzyl ether protecting group within **33** was a methyl ether instead, the average yield for the two-step sequence was approximately 65%. This

Scheme 8. Synthesis of Key Cyclization Precursor **51** and Attempted PIDA Induced Cascade.



Reagents and Conditions: a) Me_3SI, *n*-BuLi, THF, 0 ºC, 1 h; b) ZnI_2, benzene, 25 ºC, 5 min, 80% from **33**; c) 4-OMe-PhMgBr, THF, 25 ºC, 10 min, 83%; d) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 25 ºC, 30 min, 78%; e) BCl_3, CH_2Cl_2, -78 ºC, 20 min; f) $LiAlH_4$, THF, 25 ºC, 5 min, ~15%* from **49**. *Yield approximated due to product instability/impurity.

outcome is attributed to the slightly greater donating capacity of the aryl methoxy group versus a benzyloxy group,[25] a property which could induce premature opening of the intermediate epoxide (**46**) and lead to decomposition pathways. It is no surprise given the electronic environment surrounding this spiroepoxide moiety that it would be prone to opening and thus needed to be carried forward immediately. Under the more controlled circumstances of ZnI_2 treatment in benzene with the Lewis acid capturing some of the electron density on the oxygen, rearrangement to the corresponding aldehyde proceeded smoothly. Finally, Grignard addition

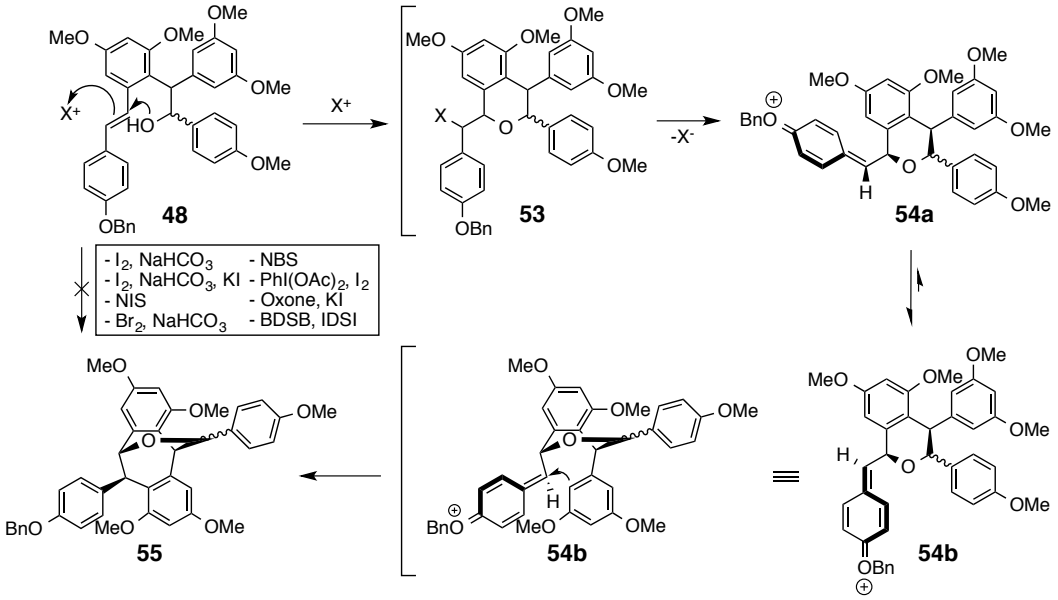
was accomplished without incident to produce cascade precursor **48** as a mixture of diastereomers.

At this stage, the quest for an ideal set of oxidation conditions began. First among them was the analogous procedure to the oxidation experiment shown in Scheme 6, namely unveiling of the single free phenol via benzyl group removal and treatment with $PhI(OAc)_2$ (not shown). In practice, the actual deprotection proved to be challenging as hydrogenation of the substrate readily reduced the alkene and acidic conditions lead to decomposition, likely through ionization of the benzylic alcohol. The desired substrate was ultimately obtained (Scheme 8), albeit in very low yield, by the three-step process of oxidation of **48** to the corresponding ketone **49**, benzyl ether cleavage using BCl_3 to give **50**, and then reduction back to the alcohol (**51**). Unfortunately, after finally obtaining this cyclization precursor, treatment with $PhI(OAc)_2$, or its more reactive congener $PhI(TFA)_2$, only afforded decomposition; no **52** was recovered, nor any characterizable products obtained. Mechanistically (Scheme 6), when one of these reagents bonds to the free phenol, an equivalent of acid, either AcOH or TFA, is produced. It seems reasonable that this equivalent of acid could have protonated the benzylic alcohol of **51** to generate a stabilized benzylic cation after expulsion of water, thereby rendering the substrate ineligible for the desired outcome and open to numerous decomposition pathways instead.

At this point, we turned to an alternate mode of reaction initiation, that of electrophilic halogen sources. Given the vast selection of halo-etherification protocols in the literature this seemed a reasonable approach. Fundamentally, the cascade was projected to work in a similar manner with the specific mechanistic steps outlined in Scheme 9. Treatment with the halonium source was hoped to induce halo-etherification to produce six membered ring intermediate **53**. At this point it was projected that the resulting benzylic halide would be expelled to give

stabilized cation **54** with free rotation about the indicated bond. Crude modeling using plastic model kits suggested that the lower rotamer **54b** would be favored due to steric interaction in **54a** between the two indicated aromatic rings. Despite the desired rotamer apparently being thermodynamically lower in energy, we recognized that this feature does not necessarily guarantee its status as the reactive isomer based on the tenets of the Curtin-Hammett principle.[26]

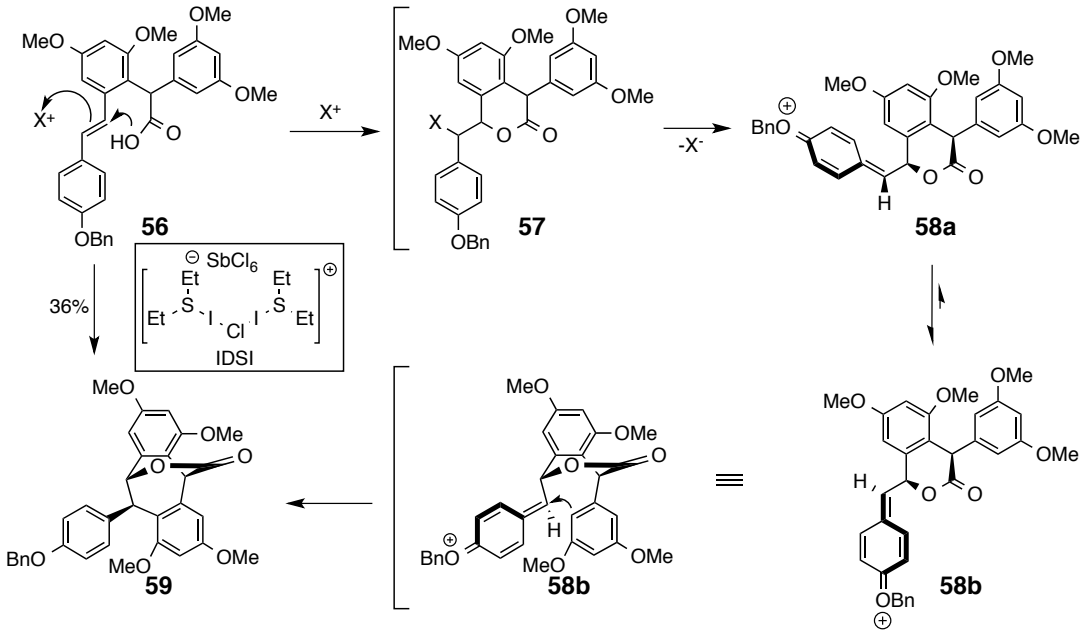
Scheme 9. Proposed Halonium Induced Double Cyclization of Tetraaryl Alcohol **51**.



Specifically the more stable intermediate may require a higher activation barrier, thus rendering it a kinetically less-favored reaction pathway. However, should **54b** proceed, then it should close the final bond to give the product **55**. Testing this approach, in the forward direction, two primary outcomes were observed: 1) halogenation of the very electron-rich aromatic rings through EAS pathways and 2) complete decomposition. Shown in the insert box within Scheme 9 is a sampling of the conditions attempted for this transformation; none produced the desired product.[27] Aromatic halogenation occurred with several of the brominating reagents and came as no surprise given that these rings are highly electron-rich and bromination is known to proceed quickly in such events as compared to iodination.[28] Regarding the decomposition, we postulated

that this outcome was due to the same acid sensitivity assumed in the previous attempts using $PhI(OAc)_2$ (Scheme 8). Many of these electrophilic halogen sources produce some type of acid which can then protonate the oxygen atom of intermediates **53** and **54** and result in C-O bond cleavage with accompanying decomposition. As such, an oxygen nucleophile without acid sensitivity was needed. With this in mind, we moved to carboxylic acid **56** which was synthesized from the preceding aldehyde in 85% yield (**47**, Scheme 8) using a Pinnick oxidation.[29] Shown in Scheme 10, there would be no mechanistic change to the overall process

Scheme 10. Successful Halonium Induced Double Cyclization of Carboxylic Acid **56**.

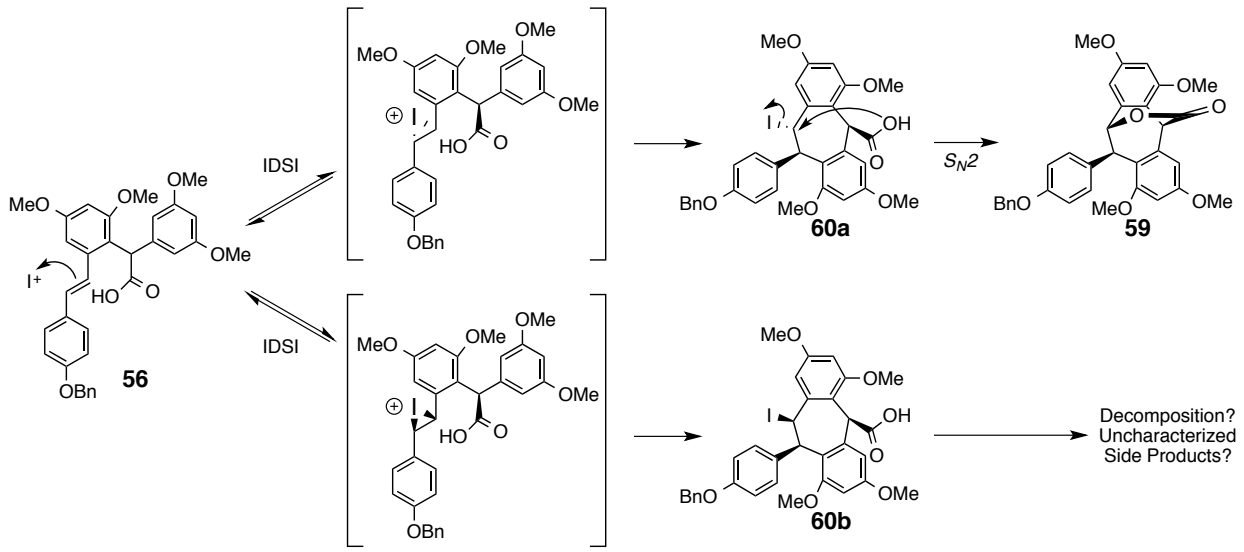


envisioned, only the notion that if the issue in the failure of the tetra-aryl alcohol was that of instability to acid, this new approach should remedy it. Resubmitting now this carboxylic acid (**56**) to the same gamut of electrophilic halogen sources, we were very pleased to find that the oxidative double cyclization was successful and bridging lactone **59** could be obtained. Three sets of conditions were found to accomplish this transformation with the two literature procedures (I_2/KI/Oxone and PIDA/I_2),[27d,e] both generating an RO-I species *in situ*. Other well-established halolactonization conditions failed to deliver the desired product. The third, and

most successful, reagent was IDSI.[30] This reagent had been developed previously in the Snyder laboratory and found its primary utility in initiating cation-π cascades on steroid-like frameworks. Not only was the entire [3.2.2] bicycle generated in this single reaction process, a feat as of yet unaccomplished in the course of this project, but the product contained the requisite all-*syn* stereochemistry among the three chiral centers and left a single functional handle, the carbonyl, for installation of the fourth and final aromatic ring.

At this point, we must acknowledge a measure of ambiguity as to the exact order of events in the above described cascade (Scheme 10). It is entirely conceivable, especially considering the precedent for seven membered ring formation in earlier substrates (Schemes 4-6), that in fact the iodonium formation, once added intermediate **56**, was attacked by the aromatic nucleophile to first form a seven membered ring such as **60a** (Scheme 11). This would deliver a secondary iodide which could then be displaced by the carboxylic acid moiety in a straightforward S_N2 type mechanism giving the desired lactone **59**. On the contrary, **60b** could be formed through a diastereomeric iodonium ion which would not be equipped for S_N2 displacement of the halide and would thus engage in alternate pathways leading to

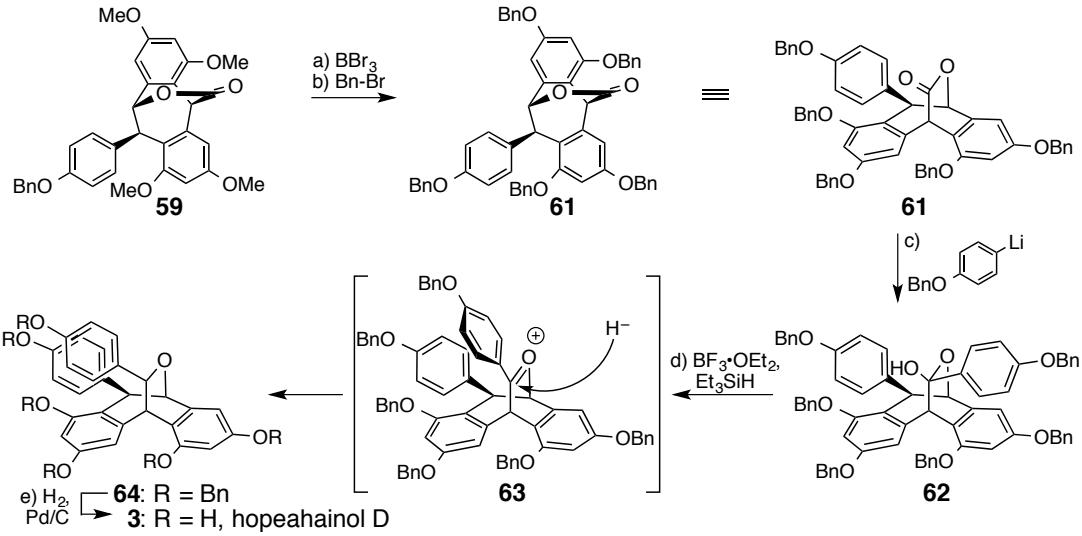
Scheme 11. Alternate Mechanism For Formation of **59**.



decomposition or other side products. The rapid iodonium transfer of such processes would likely determine diastereomeric ratio thermodynamically.[31] No obvious features in the substrate appear to encourage one diastereomer over the other and, considering the 36% yield for this transformation, it is likely that this explains the ultimate fate of the balance of the material. With the desired lactone being the only isolated product, confirmation of the active pathway(s) is all but impossible.

Pressing forward, the lactone intermediate **59** also provided a solution for another of the key concerns associated with synthesizing these molecules, namely the issue of protecting groups. As mentioned earlier, methyl ether protecting groups were essential for the success of early stage chemistry, but the harsh conditions generally required for their removal would not likely be amenable to the acid labile nature of a bis-benzylic ether such as the one present in the final targets. Gratifyingly, the bicyclic lactone **59** provided a scaffold robust enough to withstand such conditions and thus benzyl ethers were globally installed over two steps to give **61** (Scheme 12) in 80% yield. We note that despite our disappointment at the oxidative cascade

Scheme 12. Completion of the Total Synthesis of Hopeahainol D.



Reagents and Conditions: a) BBr_3, CH_2Cl_2, 25 ºC. 24 h; b) BnBr, K_2CO_3, *n*-Bu_4NI, acetone, reflux, 12 h, 89%; c) 4-benzyloxy-bromobenzene, *n*-BuLi, THF, -78 ºC, 20 min; d) BF_3•OEt_2, Et_3SiH, CH_2Cl_2, -78 ºC - 25 ºC, 10 min, 57% from **61**; e) H_2, Pd/C, EtOAc/MeOH, 25 ºC, 12 h, 79%.

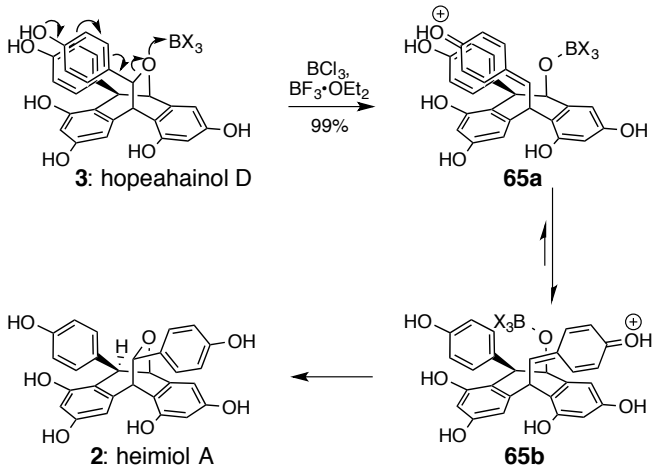
being unsuccessful with tetra-aryl alcohol **48** (see Scheme 9), the product of that reaction would already have a bis-benzylic ether installed and thus would have likely been problematic with regard to final deprotection. As such, the cyclization of carboxylic acid **56** to lactone **59** would stand as the preferred route anyway, had they both worked.

Pressing forward, lactone **61** has been redrawn within Scheme 12 to make more clear the steric influence imputed by the *para*-substituted ring with reference to the subsequent steps of the sequence. As shown in the alternative view, that ring effectively prevents incoming nucleophiles from approaching the left side of the molecule upon attack of the lactone carbonyl. This fact is illustrated in the single diastereomeric product isolated from aryl lithium addition to generate hemiketal **62**.

With the synthesis nearly complete, all that remained was reduction to furnish the bridging ether. This event proceeded smoothly using BF_3•OEt_2 as the Lewis acid and Et_3SiH as the hydride source in 57% over the two steps from lactone **61**. Critically, the incoming hydride also approaches exclusively from the less hindered face of cationic intermediate **63**, thus forcing the newly added aryl ring onto the same side of the ether bridge as the other *para*-substituted ring. By this approach, the less thermodynamically favored hopeahainol D (**3**) was formed, after global deprotection, by invoking the steric bias in the substrate to make it the kinetically favored product. In order to achieve a synthesis of heimiol A (**2**) as well, that same stereocenter required epimerization, and based on the calculation of ground state energies discussed in Section 2.2, it was believed that placing that center under thermodynamic control would then favor heimiol A (**2**). This theory was reduced to practice by treatment of hopeahainol D (**3**) with BF_3•OEt_2 and BCl_3 in MeOH, an operation which delivered heimiol A cleanly through open intermediate **65**

leaving no detectable trace of hopeahainol D (Scheme 13). It is interesting to note that neither of these two reagents alone delivered any heimiol A. Accounting for the possibility that BCl_3 may

Scheme 13. Isomerization of Hopeahainol D to Heimiol A.



just be creating HCl *in situ*, BF_3•OEt_2 and HCl were also attempted, but ultimately the two boron reagents in concert uniquely accomplished this final transformation. Only by taking the synthetic route through bicyclic lactone **59** could this inherent steric bias have been exploited twice, once to favor the kinetic product hopeahainol D (**3**) and once to favor the thermodynamic product heimiol A (**2**), ultimately delivering each of these natural products with complete selectivity. We believe this finding lends credence to the hypothesis that hopeahainol D may be the biosynthetic precursor of heimiol A.

2.5 Unexpected Results

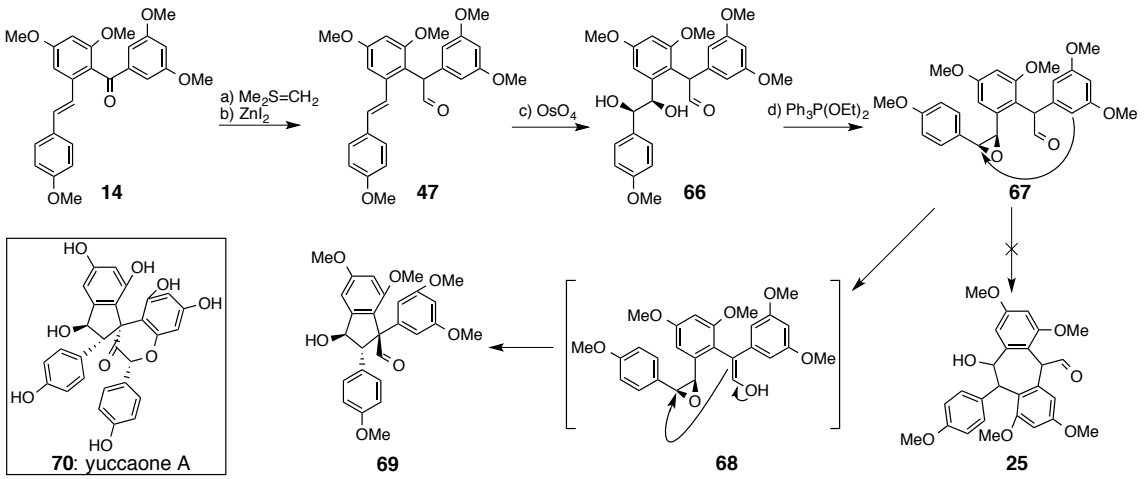
So common are undesired results in natural product synthesis that there is a great tendency to leave them unexplored. The goal of a project often directs the research toward a single target or set of related targets, and 100% of the research effort is often dedicated to this end. While the sheer volume of unexpected results is prohibitively large for a thorough investigation of each one within a given synthesis, there is a great wealth of precedent for the

value of pursuing them. As a specific example, H. C. Brown recalls, "In the course of these studies of selective reductions, a minor anomaly resulted in the discovery of hydroboration." This work led to him being honored with the Nobel prize in 1979.[32] A cursory triage of "failed" experiments may deliver a manageable pool from which to draw valuable knowledge and understanding, with academia providing an ideal environment for such exploration. It is under this pretense that the following three examples of unexpected, but interesting, results are presented as they were uncovered unexpectedly during the course of the total synthesis of heimiol A and hopeahainol D and may have value in future exploration.

2.5.1 A Route To The Core of Yuccaone A

One prevailing theory regarding the previously-described recalcitrance of ketone **14** towards cyclization of its corresponding epoxide was that the withdrawing capacity of its ketone diminished the nucleophilicity of the aromatic ring such that attack onto the epoxide was kinetically much slower. Knowing that the ketone would eventually need to be homologated to its corresponding aldehyde, this process was performed prior to cyclization to give **47** in Scheme

Scheme 14.Unexpected Cyclization Leading to Yuccaone A Core.



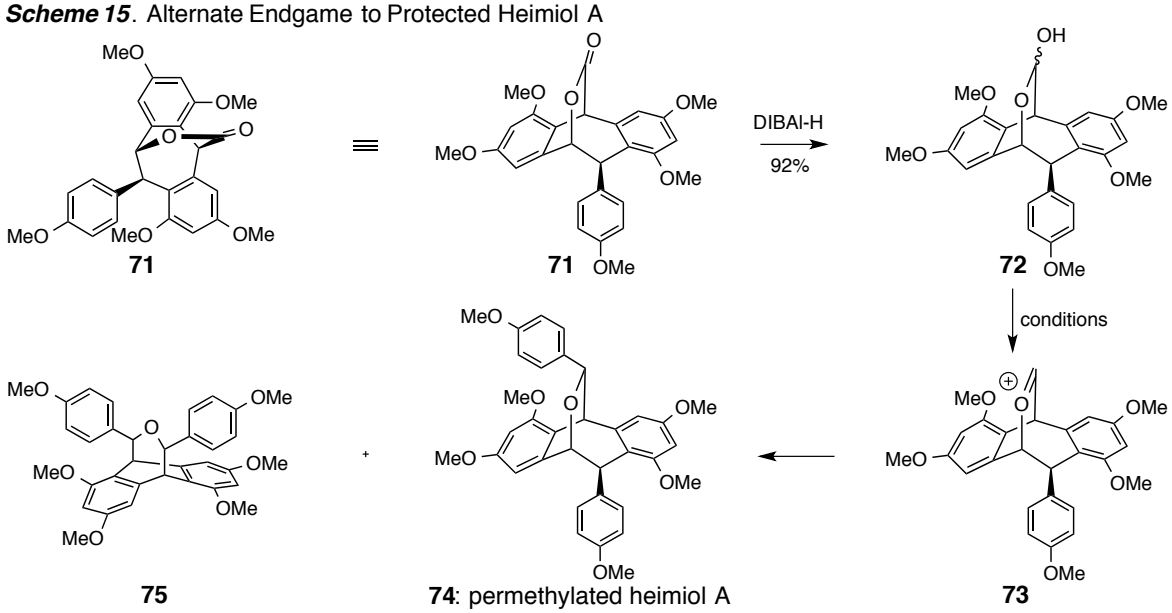
Reagents and Conditions: a) Me_3SI, *n*-BuLi, THF, 0 ºC, 1 h; b) ZnI_2, benzene, 25 ºC, 5 min, 80% from **33**; c) OsO_4, NMO, acetone/H_2O, 25 ºC, 1 h; d) $Ph_3P(OEt)_2$, tol., 70 ºC, 36 h, 22% from **47**.

14, hoping that this alteration would liberate sufficient electron density for the desired seven membered ring cyclization. The main ^{1}H NMR indicator sought in the products of this reaction was disappearance of one of the three proton signals from the 3,5-dimethoxy substituted aromatic ring to show that it had indeed attacked. In treating diol **66** with $Ph_3P(OEt)_2$ to generate the epoxide **67**, and hopefully induce the desired cyclization pathway to **25**, a single major product was identified at the end of the process. It was clear from its signature triplet (1H) proton signal that the 3,5-dimethoxy ring had not been involved. Given that this product was favored by a large margin over anything else in the mixture, the decision was made to divert a brief amount of time to purify and characterize it. As a result, we eventually determined that the epoxide had formed and was primed for nucleophilic attack, but it was the enol form of the aldehyde (**68**) that proved to be the more potent internal nucleophile, reacting instead of the aromatic ring, to form hydroxy-aldehyde **69** with a newly formed quaternary center. Pleased to have uncovered the outcome of this reaction, the carbon skeleton of this product was found to have a striking resemblance to the natural product yuccaone A (**70**),[33] a resveratrol/flavonoid hybrid isolated in 2002 having decent levels of antioxidant activity.[34] From this discovery, a new project was begun which attracted the efforts of Kazuki Sakata (a visiting scholar) and Katharina Shaw (an undergraduate researcher) who made great strides towards yuccaone A. Unforeseen issues in the endgame have complicated the synthesis; nevertheless this unexpected result uncovered a method for installing a challenging quaternary center and the effort to complete this synthesis continues.

2.5.2 Symmetric Dimer

The initial endgame pursued to complete heimiol A and hopeahainol D from lactone **71** involved a different installation of the final aromatic ring. Specifically, lactone **71** was reduced to a lactol (**72**) in 92% yield using DIBAl-H after which it was exposed to a Lewis acid (Scheme 15). This process was performed using anisole as a solvent in the hope that it would attack the newly generated oxonium ion in a Friedel-Crafts reaction to give permethylated heimol A (**74**). The initial test of this reaction was conducted overnight and an interesting outcome resulted, wherein the crude product mixture clearly indicated a fair amount of decomposition, yet one new compound was quite prominent. This product initially did not appear to have sufficient peaks to

Scheme 15. Alternate Endgame to Protected Heimiol A



Entry	Lewis Acid	Temp.	Time	Solvent	Yield	75:76
1	$AlCl_3$	25 °C	12 h	anisole	~25%	0:100
2	$AlCl_3$	25 °C	2 min	anisole	80%	2:1
3	$AlCl_3$	-30 °C	2 min	anisole	84%	100:0
4	$AlCl_3$	25 °C	2 min	10:1 anisole:DCM	92%	0:100

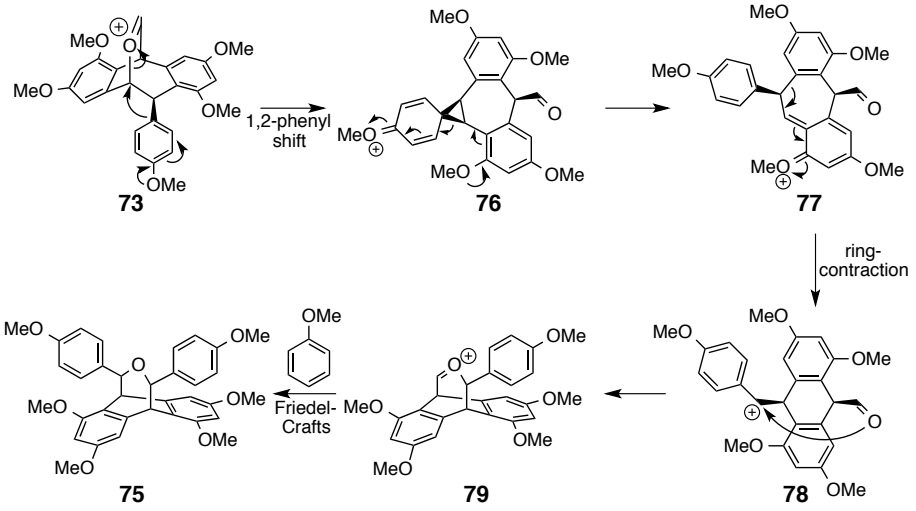
account even for its relationship to the starting material, let alone the aryl ring adduct, and upon isolation and purification we found this to be true. In fact, the NMR spectra accounted for

exactly half of the necessary peaks for successful addition of the fourth aryl ring, yet, mass spectrometry confirmed it to have the same mass as the desired product (permethylated heimiol A **75**). We therefore concluded that it was an oxidized, symmetric dimer of resveratrol whose structure we assigned to be **75** resulting from a skeletal rearrangement of the starting material.

In rerunning this experiment to confirm the result, we noticed that it is in fact complete in only two minutes and when quenched after that brief time the reaction is actually quite clean. From this second attempt, a 2:1 mixture of permethylated heimiol A and the symmetric dimer was isolated in 80% combined yield, showing that, while both products are formed initially, prolonged exposure to $AlCl_3$ effects the decomposition of **74** while leaving **75** intact. On the assumption that permethylated heimiol A formed according to our initial hypothesis and symmetric dimer **75** resulted from a skeletal rearrangement prior to Friedel-Crafts attack, we sought to uncover conditions that would favor each pathway selectively. Given the inclination towards **74**, as indicated by it being favored in a 2:1 margin with our initial conditions, the same reaction was run at lower temperature hoping this would amplify that selectivity. This approach succeeded, and by conducting the same experiment at -30 ^{o}C, as opposed to 25 ^{o}C, the protected natural product was isolated in 84% yield with no trace of the symmetric dimer. Given that a temperature drop of approximately 50 ºC would not alone account for such a drastic increase in selectivity, we are left to conclude that a change in the entropy term associated with these transformations also takes place upon lowering the temperature. This material was used to confirm our initial hypothesis that methyl ether cleavage of the final product was not feasible as swift decomposition was observed. Conversely, since the symmetric dimer **75** likely resulted from a rearrangement of the preceding oxonium intermediate **73** and that rearrangement competed with the Friedel-Crafts attack of anisole, dilution of the anisole present in solution was

expected to allow more time for the rearrangement to occur prior to attack. Indeed, altering the initial conditions to a 10/1 mixture of CH_2Cl_2/anisole as solvent instead of pure anisole afforded the symmetric dimer **75** in 92% isolated yield. Interestingly, BBr_3 promoted removal of the methyl ether groups within **75** proceeded in nearly quantitative yield (not shown). Our mechanistic hypothesis regarding the formation of **75** is shown in Scheme 16. It is thought that a

Scheme 16. Proposed Mechanism to Symmetric Dimer **75**.

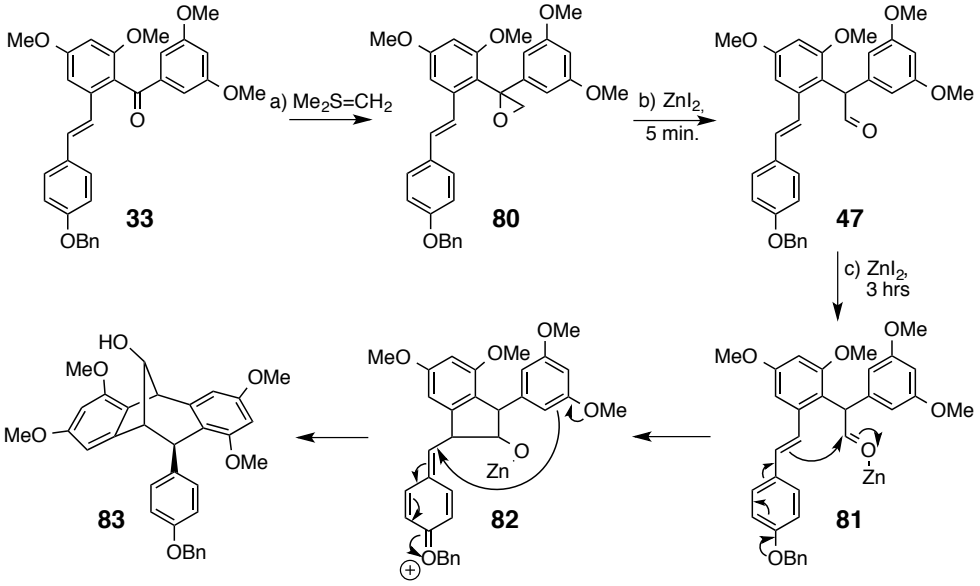


1,2-phenonium shift opens the oxonium bridge of **73** to reveal aldehyde **77**, an intermediate possessing a highly stabilized benzylic carbocation. At this point, ring contraction to the generally more favored six membered ring could produce intermediate **78**, also with a stabilized cation, after which the bridge was reformed (**79**) and a terminating Friedel-Crafts attack from the side of the bridge opposite the existing *para*-substituted ring produced C_{2v}-symmetric **75**. Had the initial experiment that generated only the symmetric dimer been dismissed as mere decomposition due to missing NMR signals, the insight gained into this fascinating skeletal rearrangement as well as the unique approach to protected heimiol A would have remained undiscovered.

2.5.3 Constrained Ampelopsin F and Gnetuhainin C Analogues

Lastly, in our survey of fortuitous events outside of those initially intended, comes the ZnI_2-induced rearrangement of epoxide **80** (Scheme 17). With analogous operations having been performed on other substrates, we had become accustomed to this transformation requiring approximately one hour for completion. Following initiation of the protocol with ZnI_2, the reaction was checked by TLC after approximately 30 minutes, at which point complete consumption of the starting material was observed with the presence of at least two new compounds, one being favored over the other. Pleasingly, the more abundant product was quickly identified as the desired aldehyde **47**, while the other no longer possessed alkene signals

Scheme 17. Unexpected Formation of [3.2.1] Bicycle **83**.

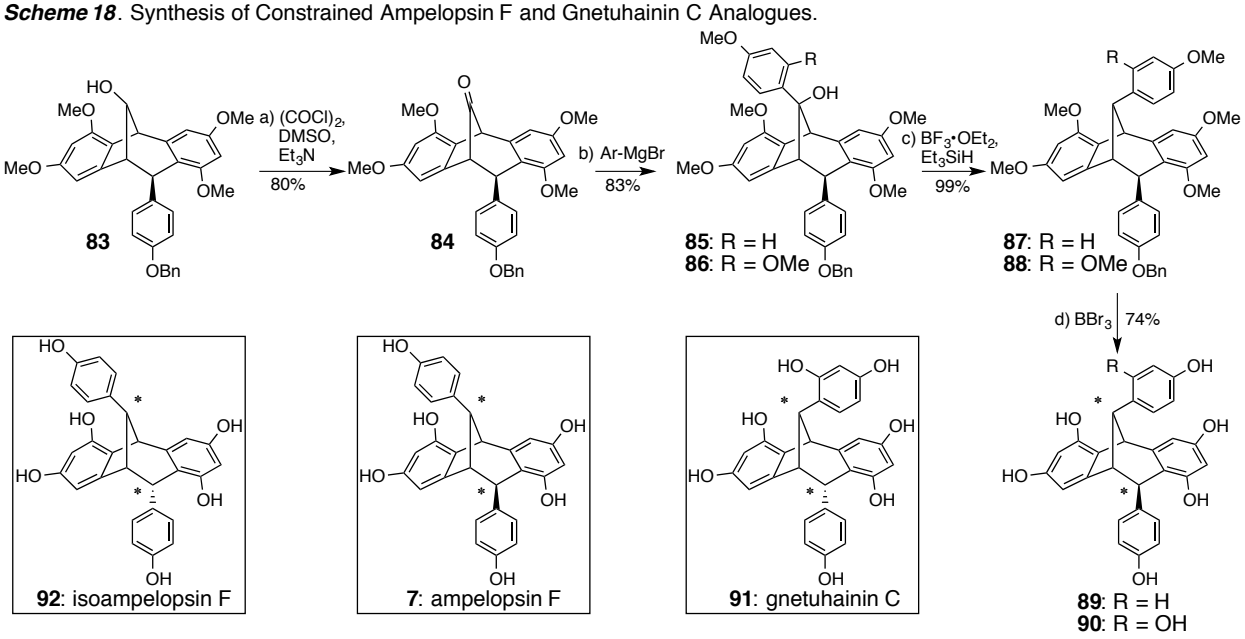


Reagents and Conditions: a) Me_3SI, *n*-BuLi, THF, 0 ºC, 1 h; b) ZnI_2, benzene, 25 ºC, 5 min, 80% from **33**; c) ZnI_2, benzene, 25 ºC, 3 h, 63% from **33**.

and revealed a new bond formation involving the 3,5-dimethoxy substituted ring. Closer monitoring of the reaction on subsequent experiments showed that the epoxide starting material converted completely to the aldehyde **47** and that prolonged exposure to the reaction conditions then converted that into the unknown, second product. With this information, we were able to discern this unexpected side product as [3.2.1] bicycle **83**, its formation likely catalyzed by ZnI_2-

activation of the aldehyde towards attack by the olefin to first give five membered ring intermediate **82**. This species then underwent a second cyclization to furnish the final product; this material could ultimately be produced directly from the epoxide in 64% yield by prolonged ZnI_2 exposure. Carrying this forward in much the same way as lactone **61** (see Scheme 12), the alcohol was oxidized to ketone **84** after which Grignard addition, alcohol reduction, and deprotection gave compounds **89** and **90** (Scheme 18). The [3.2.1] bicycle of this product is well represented by resveratrol dimers in the literature. In fact, while conserving the bicycle itself, four possible diastereomers are possible by varying the two marked stereocenters associated with

Scheme 18. Synthesis of Constrained Ampelopsin F and Gnetuhainin C Analogues.



Reagents and Conditions: a) $(COCl)_2$, DMSO, CH_2Cl_2, -30 ºC - 25 ºC, 1 h, then Et_3N, 80%; b) 4-OMe-PhMgBr, THF, 25 ºC, 20 min, 83%; c) BF_3•OEt_2, Et_3SiH, CH_2Cl_2, 25 ºC, 10 min, 99%; d) BBr_3, CH_2Cl_2, 25 ºC, 24 h, 74%.

the *para*-substituted aromatic rings, three of them corresponding to natural products (Scheme 18).[35] The above described synthesis very effectively delivers the fourth, non-natural diastereomer and efforts to epimerize either of the *para*-substituted rings through an acid-induced retro Friedel-Crafts/Friedel-Crafts sequence[36] or hydride abstraction and re-addition of either of the drawn hydrogens to a more thermodynamically favored product using a trityl cation failed.[37] Nonetheless, by investigating this initially minor side product we were able to discover

a unique, double cyclization cascade and accomplish the synthesis of highly strained natural product analogues. Furthermore, the intermediates obtained en route to **89**/**90** have served as highly informative scaffolds for investigations into the regioselectivity of BDSB enabled aryl bromination versus conventional brominating reagents (see Scheme 13, Chapter 1).[38]

2.6 Conclusion

In summary, we have accomplished the first reported total synthesis of the natural products heimiol A (**2**) and hopeahainol D (**3**) in ten steps and 9.7% yield and 9 steps and 9.8% yield, respectively, from the known Snyder group common intermediate ketone **33**. Key to this sequence was the development of a unique, oxidative double cyclization cascade to form the entirety of the [3.2.2] bicyclic core of the natural products with the requisite all-*syn* stereochemistry about the base seven membered ring in one fell swoop. Inherent steric influence in the substrate was exploited to deliver the two natural products in turn and with complete selectivity. Select examples of unanticipated results were investigated to yield a number of interesting discoveries and related projects.

Acknowledgements

Mr. Jason Pflueger is acknowledged for invaluable assistance during the course of the entire project, particularly the preparation of intermediates, initial screening of halolactonization conditions, and preparing a sample of lactone **71** for X-ray crystallographic analysis. Dr. Steven Breazzano is acknowledged for earlier synthetic work towards heimiol A (not included in this chapter). Prof. Gerard Parkin, Dr. Wesley Sattler and Dr. Aaron Sattler are thanked for X-ray crystallographic analysis of noted intermediates. Dr. Yasuhiro Itagaki is acknowledged for mass

spectrometric analysis. Dr. John Decatur and Mr. Michael Appel are acknowledged for NMR assistance.

2.7 References

1. J.-F. F. Weber, I. A. Wahab, A. Marzuki, N. A. Thomas, A. A. Kadir, A. H. A. Hadi, K. Awang, A. A. Latiff, P. Richomme, J. Delaunay, *Tetrahedron Lett.* **2001**, *42*, 4895 – 4897.

2. E. H. Sahidin, L. D. Juliawaty, Y. M. Syah, L. Din, E. L. Ghisalberti, J. Latip, I. M. Said, S. A. Achman, *Z. Naturforsch. C* **2005**, *60*, 723 – 727.

3. a) S. Atun, S. A. Achmad, M. Niwa, R. Arianingrum, N. Aznam, *Biochem. Syst. Ecol.* **2006**, *34*, 642 - 644; b) S. Atun, N. Aznam, R. Arianingrum, Y. Takaya, N. Masatake, *J. Phys. Sci.* **2008**, *19*, 7 – 21.

4. H. M. Ge, W.-H. Yang, J. Zhang, R.-X. Tan, *J. Agric. Food Chem.* **2009**, *57*, 5756 – 5761.

5. T. Yan, T. Wang, W. Wei, N. Jiang, Y. H. Qin, R. X. Tan, H. M. Ge, *Planta Medica* **2012**, *78*, 1015 - 1019.

6. M. N. C. Diyasena, S. Sotheeswaran, S. Surenrakumar, S. Balasubramanian, M. Bokel, W. Kraus, *J. Chem. Soc. Perkin T 1* **1985**, *8*, 1807 - 1809.

7. Y. H. Qin, J. Zhang, T. Jiang, Z. K. Guo, N. Jiang, R. X. Tan, H. M. Ge, *RSC Advances* **2011**, *1*, 135 - 141.

8. L. D. Juliawaty, Sahidin, E. H. Hakim, S. A. Achmad, Y. M. Syah, J. Latip, I. M. Said, *Nat. Prod. Comm.* **2009**, *4*, 947 - 950.

9. D. M. Bollag, P. A. McQueney, J. Zhu, O. Hensens, L. Koupal, J. Liesch, M. Goetz, E. Lazarides, C. M. Woods, *Cancer Res.* **1995**, *55*, 2325.

10. (a) S. A. Snyder, A. L. Zografos, Y. Lin, *Angew. Chem. Int. Ed.* **2007**, *46*, 8186 - 8191; (b) S. A. Snyder, S. P. Breazzano, A. G. Ross, Y. Lin, A. L. Zografos, *J. Am. Chem. Soc.* **2009**, *131*, 1753 - 1765.

11. (a) Ortiz de Montellano,P. R., *Cytochrome P-450 Structure, Mechanism, and Biochemistry;* Plenum: New York, **1986.** (b) Guengerich, F. P.; Macdonald, T. C. *Ace. Chem. Res.* **1984**, *17*, 9. **(c)** M. Morales, J. Alcantara, A. Ros Barcelo, *Am. J. Enol. Vitic.* **1997**, *48*, 33 - 38.

12. (a) K. C. Nicolaou, R. T. Wu, Q. Kang, D. Y.-K. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 3340 - 3343; (b) J. L. Jeffrey, R. Sarpong, *Org. Lett.* **2009**, *11*, 5450 - 5453; (c) B. Chen, J.-P. Lu, X.-G. Xie, X.-G. She, X.-F. Pan, *Chin. J. Org. Chem.* **2006**, *26*, 1300 - 1302.

13. T. Tanaka, T. Ito, K.-I. Nakaya, M. Iinuma, Y. Takahashi, H. Naganawa, S. Riswan; *Heterocycles* **2001**, *55*, 729 - 740.

14. D. B. Dess, J. C. Martin *J. Org. Chem.* **1983**, *48*, 4155 - 4156.

15. R. Mello, M. Fiorentino, O. Sciacovelli, R. Curci *J. Org. Chem.* **1988**, *53*, 3890 - 3891.

16. See as representative examples of benzylic oxidation methods: (a) R. Rangarajan, E. J. Eisenbraun, *J. Org. Chem.* **1985**, *50*, 2435 - 2438; (b) J.-Q. Yu, E. J. Corey, Org. Lett. 2002, 4, 2727 – 2730 ; c) J.-Q. Yu, E. J. Corey, J. Am. Chem. Soc. 2003, 125, 3232 – 3233. (d) Becker, H.-D.; , *J. Org. Chem.* **1965,** *30,* 982. (e) Findlay, J. W. A.; Turner, A. B., *J. Chem. Soc. (C)* **1971,** 547.

17. T. K. M. Shing, Y.-Y. Yeung, P. L. Su, *Org. Lett.* **2006**, *8*, 3149 - 3151.

18. C. E. Coburn, D. K. Anderson, J. S. Swenton, *J. Org. Chem.* **1983**, *48*, 1455.

19. V. VanRheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976**, *23*, 1973 - 1976.

20. J. W. Kelly, S. A. Evans Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7681 - 7685.

21. P. L. Robinson, C. N. Barry, J. W. Kelly, S. A. Evans Jr. *J. Am. Chem. Soc.* **1987**, *109*, 5210 - 5219.

22. A. Pelter, S. Elgendy, *Tet. Lett.* **1988**, *29*, 677.

23. E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353 - 1364.

24. J. Meinwald, S. S. Labana, M. S. Chadha, *J. Am. Chem. Soc.* **1963**, *85*, 582.

25. L. P. Hammett, *J. Am. Chem. Soc.* **1937**, *59*, 96 - 103. (Note: Though not directly compared, we believe the data presented herein supports our claim.)

26. Carey, Francis A.; Sundberg, Richard J.; (1984). *Advanced Organic Chemistry Part A Structure and Mechanisms (2nd ed.)*. New York N.Y.: Plenum Press.

27. (a) M. D. Dowle, D. I. Davies, *Chem. Soc. Rev.* **1979**, *8*, 171 - 197; (b) K. C. Majumdar, P. K. Basu, *Synth. Commun.* **2002**, *32*, 3719; (c) E. Demole, P. Enggist, *Helv. Chim. Acta* **1971**, *54*, 456; (d) M.Curini,F.Epifano,M.C.Marcotullio,F.Montanari,Synlett 2004, 368 – 370 ; (e) H. Gottam, T. K. Vinod, *J. Org. Chem.* **2011**, *76*, 974 – 977.

28. (a) E. B. Merkushev, *Synthesis* **1988**, 923 - 937; (b) Smith, Michael B.; March, Jerry; (2007). *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (6th ed.)*. Hoboken, N. J.: John Wiley and Sons, Inc.

29. B. O. Lindgren, T. Nilsson, *Acta Chem. Scand.* **1973**, *27*, 888 - 890.

30. S. A. Snyder, D. S. Treitler, A. P. Brucks, *J. Am. Chem. Soc.* **2010**, *132*, 14303 – 14314.

31. A. A. Neverov, R. S. Brown, *J. Org. Chem.* **1996**, *61*, 962 - 968.

32. H. C. Brown, *Science* **1980**, *210*, 485 - 492.

33. S. Piacente, G. Bifulco, C. Pizza, A. Stochmal, W. Oleszek, *Tet. Lett.* **2002**, *43*, 9133 - 9136.

34. S. Piacente, P. Montoro, W. Oleszek, C. Pizza, *J. Nat. Prod.* **2004**, *67*, 882 - 885.

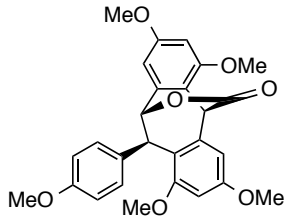
35. (a) Y. Oshima, Y. Ueno, K. Hisamichi, M. Takeshita, *Tetrahedron* **1993**, *49*, 5801 - 5804; (b) T. Tanaka, M. Ohyama, K. Morimoto, F. Asai, M. Iinuma, *Phytochemistry* **1998**, *48*, 1241 - 1243; (c) K.-S. Huang, Y.-H. Wang, R.-L. Li, M. Lin, *J. Nat. Prod.* **2000**, *63*, 86 -89.

36. For examples of a retro Friedel-Crafts reaction see: (a) N. J. Hales, H. Heaney, J. H. Hollinshead, R. P. Sharma, *Tetrahedron* **1995**, *51*, 7403 - 7410; (b) J. P. Bacci, A. M. Kearney, D. L. Van Vranken, *J. Org. Chem.* **2005**, *70*, 9051 - 9053.

37. For a previous example of use of trityl cation as a hydride abstraction reagent see: E. Brule, Y. R. de Miguel, *Tet. Lett.* **2002**, *43*, 8555 - 8558.

38. M. I. Chiriac, P. Gan, A. Gollner, S. A. Snyder, *In Preparation.*

Relevent X-Ray Crystal Structures:



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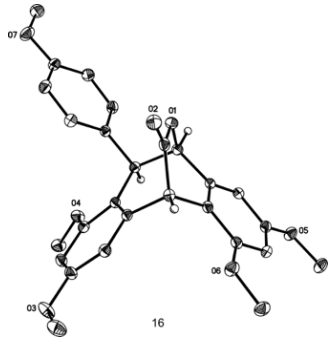

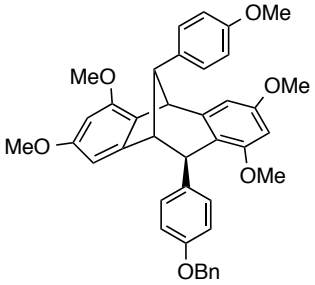

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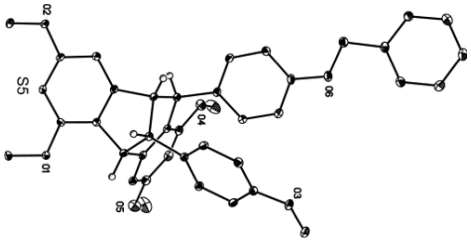


2.8 Experimental Procedures

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), acetonitrile (MeCN), toluene, benzene, diethyl ether (Et_2O) and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and either an aqueous solution of ceric ammonium sulfate and ammonium molybdate and heat or an aqueous solution of potassium permanganate and sodium bicarbonate and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-300, DRX-400, DMX-500 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, br = broad, AB = AB quartet, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using the MALDI (matrix-assisted laser-desorption ionization) technique.

Aldehyde 24. To a suspension of trimethylsulfonium iodide (0.564 g, 2.76 mmol, 10 equiv) in THF (5 mL) at 0 °C was added *n*-BuLi (1.40 mL, 1.6 M in hexanes, 2.24 mmol, 8.0 equiv). After stirring the resulting opaque pale yellow solution for 17 minutes at 0 °C, a solution of **21** (0.120 g, 0.276 mmol, 1.0 equiv) in THF (4 mL) was added dropwise over the course of 1 minute. The reaction mixture was then warmed warm to 25 °C and stirred for 14 h. Upon completion, the reaction contents were quenched by the addition water (7 mL), and extracted with EtOAc (3 × 25 mL). The combined organic layers were then washed with water (15 mL) then brine (15 mL), dried ($MgSO_4$), filtered, and concentrated. Pressing forward without any further purification, the so-obtained crude epoxide was taken up in benzene (7 mL) and ZnI_2 (0.110 g, 0.345 mmol, 1.25 equiv) was added as a single portion at 25 °C in an ambient atmosphere. Upon completion after 12 h, the reaction contents were quenched by the addition of water (7 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 1:1) to give **24** (0.089 g, 72% yield from **21**, 2.5:1 mixture of diastereomers) as a pale yellow foam. **24:** R_f = 0.60 (silica gel, 100% Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ diastereomer 1: 9.87 (s, 1 H), 7.11 (d, *J* = 8.4 Hz, 2 H), 6.78 (d, *J* = 8.7 Hz, 2 H), 6.45 (d, *J* = 2.4 Hz, 2 H), 6.39 (d, *J* = 2.4 Hz, 1 H), 6.29 (d, *J* = 2.7 Hz), 5.29 (s, 1 H), 4.25 (dd, *J* = 5.7 Hz, 12.9 Hz, 1 H), 3.82 (s, 3 H), 3.81 (s, 6 H), 3.76 (s, 3 H), 3.36 (s, 3 H), 2.99 (dd, *J* = 13.2 Hz, 14.7 Hz, 1 H), 2.82 (dd, *J* = 5.7 Hz, 15.0 Hz, 1 H); diastereomer 2: 9.77 (s, 1 H), 6.51 (s, 4 H), 6.48 (d, *J* = 2.4 Hz, 1 H), 6.36 (d, *J* = 2.7 Hz, 1 H), 6.31 (d, *J* = 2.4 Hz, 1 H), 5.61 (d, *J* = 2.4 Hz, 1 H), 5.49 (s, 1 H), 4.62 (dd, *J* = 3.0 Hz, 5.4 Hz, 1 H), 3.84 (s, 6 H), 3.67 (s, 3 H), 3.51 (s, 3 H), 3.50 (s, 3 H), 3.35 (dd, *J* = 3.0 Hz, 13.8 Hz, 1 H), 2.70 (dd, *J* = 5.4 Hz, 14.1 Hz, 1 H).

Dioxolane 27. To a solution of **24** (0.100 g, 0.223 mmol, 1.0 equiv) in a 1:1 mixture of toluene and ethylene glycol (3 mL) was added *p*-TsOH (4.0 mg, 0.022 mmol, 0.1 equiv). The reaction mixture was then warmed to 110 ºC and stirred for 1.75 h. Upon completion the reaction contents were washed with water (3 x 10 mL) after which the aqueous wash was extracted with EtOAc (20 mL) and combined with the original organic layer. The combined organic layers were washed with water (15 mL) then brine (15 mL), dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:1) to give **27** (0.089 g, 81% yield) as a white foam. **27:** R_f = 0.52 (silica gel, 100% Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ diastereomer 1: 7.09 (d, *J* = 8.6 Hz, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 6.56 (d, *J* = 2.6 Hz, 1 H), 6.39 (d, *J* = 2.4 Hz, 1 H), 6.34 (d, *J* = 2.4 Hz, 1 H), 6.26 (d, *J* = 2.4 Hz, 1 H), 5.86 (d, *J* = 7.0 Hz, 1 H), 4.87 (d, *J* = 6.9 Hz, 1 H), 4.41 (dd, *J* = 6.5 Hz, 13.1 Hz, 1 H), 4.05-3.76 (m, 5 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.78 (s, 6 H), 3.33 (s, 3 H), 2.87 (dd, *J* = 6.5 Hz, 14.6 Hz, 1 H); diastereomer 2: 6.66 (d, *J* = 2.5 Hz, 1 H), 6.51 (s, 4 H), 6.32 (d, *J* = 2.5 Hz, 1 H), 6.26 (d, *J* = 2.4 Hz, 1 H), 5.60 (d, *J* = 2.4 Hz, 1 H), 5.47 (d, *J* = 5.6 Hz, 1 H), 5.05 (d, *J* = 5.6 Hz, 1 H), 4.71 (dd, *J* = 2.9 Hz, 5.1 Hz, 1 H), 4.05-3.76 (m, 5 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.66 (s, 3 H), 3.49 (s, 6 H), 2.70 (dd, *J* = 5.3 Hz, 13.9 Hz, 1 H).

Alcohol 30. To a solution of **21** (0.010 g, 0.023 mmol, 1.0 equiv) in EtOAc (0.8 mL) was added 3 Å mol. sieves (0.030 g) followed by TBHP (0.021 mL, 5.5 M in decane, 0.115 mmol, 5.0 equiv) and the resulting solution stirred for 30 min at 25 ºC. $Mn(OAc)_3$•$2H_2O$ (0.6 mg, 0.002 mmol, 0.1 equiv) was then added as single portion and the resulting solution stirred at 25 ºC for 21 h. Upon completion the reaction contents were filtered through a cotton plug after which the filtrate was concentrated directly and purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to give **30** (~ 1-2 mg, ~ 10-20% yield) as a pale yellow oil. **30**: R_f =

0.30 (silica gel, 100% Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, *J* = 2.4 Hz, 1 H), 6.64 (br s, 2 H), 6.55 (d, *J* = 2.4 Hz, 1 H), 6.20 (d, *J* = 2.1 Hz, 1 H), 5.49 (br s, 1 H), 4.41 (d, *J* = 13.5 Hz, 1 H), 3.90 (s, 3 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.49 (s, 3 H), 3.44 (s, 3 H), 2.82 (d, *J* = 13.5 Hz, 1 H).

Alkene 31. To a solution of **21** (0.032 g, 0.074 mmol, 1.0 equiv) in THF (2 mL) at -78 ºC was added KO*t*Bu (0.100 mL, 1.0 M in THF, 0.100, 1.35 equiv) and the resultant solution stirred for 10 min. The argon atmosphere was then removed and replaced with O_2 (g) using vacuum after which the reaction mixture was allowed to warm to 25 ºC over the course of 12 h. Upon completion the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (1 mL), poured into water (1 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were then washed with brine (3 mL), dried ($MgSO_4$), and concentrated to give a crude mixture containing primarily the starting material **21** and the known product **31** (estimated 9.6 mg by crude ^1H NMR spectra, 30% yield). For full characterization of **31** see ref. 47, Chapter 1.

Epoxide 33. NMO (0.243 g, 2.07 mmol, 3 equiv) and OsO_4 (0.70 mL, 2.5 wt % in *t*-BuOH, 0.070 mmol, 0.1 equiv) were added sequentially to a solution of **14** (0.300 g, 0.690 mmol, 1.0 equiv) in acetone (30 mL) and water (10 mL) at 25 °C in an ambient atmosphere. The reaction flask was sealed to prevent solvent evaporation and the contents were stirred at 25 °C for 5 h. Upon completion, the reaction mixture was quenched with saturated aqueous Na_2SO_3 (1 mL), poured into water (1 mL), and extracted with EtOAc (3 × 3 mL). The combined organic layers were then washed with brine (2 mL), dried ($MgSO_4$), filtered, and concentrated. Pressing forward without any additional purification, the newly formed diol **32** (0.160 g, 0.342 mmol, 1.0 equiv) was taken up in toluene (4 mL) after which $Ph_3P(OEt)_2$ (0.375 mL, 1.0 M in toluene, 0.375 mmol, 1.1 equiv) was added. The resultant solution was warmed to 70 ºC for 72 h and,

upon completion, the reaction mixture was concentrated directly to give **33** as a pale yellow oil (~ 0.130 g, 80% yield estimated based on crude NMR). Generally, this material was carried forward without any further purification. For characterization purposes, however, the resultant yellow/orange crude oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1 → 1:1) to give **33** as a white foam. **33**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.7 Hz, 2 H), 6.94 (d, *J* = 8.7 Hz, 2 H), 6.82 (d, *J* = 2.4 Hz, 1 H), 6.81 (d, *J* = 2.4 Hz, 2 H), 6.37 (t, *J* = 2.4 Hz, 1 H), 6.31 (d, *J* = 2.4 Hz, 1 H), 4.81 (d, *J* = 2.7 Hz, 2 H), 3.82 (s, 3 H), 3.79 (s, 9 H), 3.57 (s, 3 H).

Permethylated Hemsleyanol E 13. BF_3•OEt_2 (3.0 μL, 0.022 mmol, 1.0 equiv) was added to a solution of **33** (0.010 g, 0.022 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at -78 ºC. The reaction contents were allowed to warm to 25 ºC over 1 h after which they were quenched by the addition of water (1 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were then washed with brine (2 mL), dried ($MgSO_4$), and concentrated to give **13** (~ 4.0 mg, ~ 40% yield based on crude ^{1}H NMR spectra). For full characterization of **13** see ref. 10b, Chapter 2.

Free Phenol 37. To a solution of **34** (0.458 g, 0.897 mmol, 1.0 equiv) in $MeNO_2$ (22 mL) at -20 ºC was added a solution of BDSB (0.494 g, 0.897 mmol, 1.0 equiv) in $MeNO_2$ (5 mL) and stirred for 15 min. Upon completion the reaction contents were quenched by the addition of 1:1 saturated aqueous $NaHCO_3$: saturated aqueous Na_2SO_3 (20 mL), poured into water (15 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were then dried ($MgSO_4$), concentrated, and carried on without further purification. The crude bromide **36** was dissolved in THF (25 mL) after which KOH (0.650 g, 11.6 mmol, 13.0 equiv) and 18-crown-6 (0.080 g, 0.300 mmol, 0.33 equiv) were added sequentially and as single portions. The resultant solution

was covered with tin foil and warmed to 50 ºC for 18 h. Upon completion the reaction contents were carefully quenched by the addition of saturated aqueous NH_4Cl (10 mL), poured into water (5 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 95:5 → 3:2) to give the resultant alkene (0.225 g, 49% from **34**). Pressing forward, the newly formed alkene (0.075 g, 0.147 mmol, 1.0 equiv) was dissolved in toluene (8 mL) after which *p*-TsOH (0.280 g, 1.47 mmol, 10 equiv) was added as a single portion. The resultant solution was then warmed to 80 ºC for 2 h after which the reaction contents were quenched carefully by the addition of saturated aqueous $NaHCO_3$ (5 mL), poured into water (5 mL), and extracted with EtOAc (3 x 10 mL). The combined organic layers were then washed with brine (5 mL), dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 1:1) to give **37** (0.029 g, 47% yield) as an off-white solid. **37**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 8.7 Hz, 2 H), 6.93 (s, 1 H), 6.81 (d, J = 2.7 Hz, 1 H), 6.74 (d, J = 8.4 Hz, 2 H), 6.49 (d, J = 2.4 Hz, 2 H), 6.46 (d, J = 2.1 Hz, 1 H), 5.17 (s, 1 H), 3.89 (s, 3 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.36 (s, 3 H).

Diketoaldehyde 41. To a solution of **37** (0.029 g, 0.069mmol, 1.0 equiv) in 10:1 THF : H_2O (3 mL) was added $PhI(OAc)_2$ (0.027 g, 0.083 mmol, 1.2 equiv) as a single portion at 25 ºC. The resultant solution was stirred for 45 min after which the reaction contents were quenched by the addition of water (3 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were then washed with brine (5 mL), dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 1:1) to give **41** (0.013 g, 42% yield) as an off-white solid. **41**: R_f = 0.30 (silica gel, hexanes/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1 H), 7.55 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 2.1 Hz, 1 H), 6.81 (s, 1 H), 6.79 (d,

J = 2.4 Hz, 1 H), 6.70 (d, *J* = 8.4 Hz, 2 H), 6.69 (d, *J* = 2.1 Hz, 1 H), 6.44 (d, *J* = 2.1 Hz, 1 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.69 (s, 3 H), 3.59 (s, 3 H).

Aldehyde 47. Me_3SI (4.00 g, 19.6 mmol, 10 equiv) and *n*-BuLi (11.3 mL, 1.6 M in hexanes, 17.7 mmol, 9.0 equiv) were added sequentially to THF (100 mL) at 0 °C, and then the resulting pale yellow solution was stirred for 2 min at 0 °C. A solution of ketone **33** (1.00 g, 1.96 mmol, 1.0 equiv) in THF (80 mL) was then added dropwise over the course of 10 min and the resulting mixture was allowed to stir for an additional 1 h at 0 °C. Upon completion, the reaction contents were quenched by the addition of water (50 mL) and extracted with EtOAc (3 × 75 mL). The combined organic extracts were then washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$,), filtered, and concentrated. [Note: This material is not very stable and must be carried on without delay for optimal results.] Pressing forward without any additional purification, this newly formed material was dissolved in benzene (40 mL) and ZnI_2 (0.626 g, 1.96 mmol, 1.0 equiv) added in a single portion at 25 °C. After stirring the resultant mixture for 3 to 5 min in a reaction vessel open to air, the reaction contents were quenched with water (20 mL). The resultant bi-phasic solution was stirred vigorously for 3 min and then extracted with EtOAc (3 × 40 mL). The combined organic extracts were then washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude orange oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 4/1) to afford aldehyde **47** (0.824 g, 80% yield over 2 steps) as a white foam. **47**: R_f = 0.63 (silica gel, hexanes/EtOAc, 1/1); IR (film) νmax 2939, 2838, 1721, 1600, 1457, 1322, 1242, 1155, 1063, 833; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.33 (m, 5 H), 7.32 (d, *J* = 8.8 Hz, 2 H), 7.00 (d, *J* = 16.0 Hz, 1 H), 6.93 (6, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 15.6 Hz, 1 H), 6.76 (d, *J* = 2.4 Hz, 1 H), 6.49 (d, *J* = 2.4 Hz, 1 H), 6.38 (s, 3 H), 5.08 (s, 2 H), 4.93 (s, 1 H), 3.88 (s, 3 H), 3.78 (s, 3 H), 3.74 (s, 6 H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 200.2, 161.0, 160.4, 158.9, 158.3, 140.5, 139.4, 137.0, 132.4, 130.1, 128.8, 128.2, 128.1, 127.6, 124.4, 117.1, 115.3, 107.4, 103.8, 99.0, 98.5, 70.2, 57.2, 55.9, 55.6, 55.4; HRMS (FAB+) calcd for $C_{33}H_{32}O_6^+$ [M+] 524.2199, found 524.2198.

Tetra-aryl Alcohol 48. 4-methoxy-phenylmagnesium bromide (0.95 mL, 1.0 M in THF, 0.95 mmol, 10 equiv) was added to a solution of **47** (0.050 g, 0.095 mmol, 1.0 equiv) in THF (2 mL) at 25 ºC and the resulting solution allowed to stir for 3 h. Upon completion the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (1 mL), poured into water (1 mL), and extracted with EtOAc (3 x 3 mL). The combined organic layers were then washed with brine (2 mL), dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) to give **48** (0.050 g, 83% yield) as a 1:1 mixture of diastereomers.

Tetra-aryl Ketone 49. Dess–Martin periodinane (0.140 g, 0.321 mmol, 1.2 equiv) was added to a solution of alcohol **48** (0.169 g, 0.267 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) at 25 °C, and the resultant mixture was stirred for 30 min in an ambient atmosphere. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous Na_2SO_3 (4 mL) and stirred vigorously for 5 min at 25 °C. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ (4 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to give **49** (0.132 g, 78%) as a yellow/orange foam. **49**: R_f = 0.50 (silica gel, hexanes/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.7 Hz, 2 H), 7.46-7.34 (m, 7 H), 7.25 (d, *J* = 15.9 Hz, 1 H), 6.97 (d, *J* = 8.7 Hz, 2 H), 6.84 (d, *J* = 15.9 Hz, 1 H), 6.75 (d, *J* = 9.0 Hz, 3 H), 6.46 (d, *J* = 2.1 Hz, 2 H), 6.40 (t, *J* = 2.1 Hz, 1 H), 6.38 (d, *J* = 2.1 Hz, 1 H), 5.98

(s, 1 H), 5.08 (s, 2 H), 3.83 (s, 3 H), 3.76 (s, 9 H), 3.65 (s, 3 H).

Alcohol 51. BCl_3 (0.42 mL, 1.0 M in CH_2Cl_2, 0.42 mmol, 3.0 equiv) was added to a solution of **49** (0.088 g, 0.140 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) at -78 °C. After stirring for 20 min at -78 °C, the reaction contents were allowed to warm to 25 ºC then quenched by the slow, careful addition of saturated aqueous $NaHCO_3$ (3 mL), poured into water (3 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), filtered, concentrated, and carried on without further purification. This newly formed phenol **50** was slowly added as a solution in THF (2 mL) to a suspension of $LiAlH_4$ (0.010, g, 0.280 mmol, 2.0 equiv) in THF (1 mL) at 25 ºC and allowed to stir for 5 min. Upon completion the reaction contents were quenched by the slow, careful addition of saturated aqueous NH_4Cl (1 mL), poured into water (3 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:2) to give **51** (~ 0.012 g, 15% yield) as a mixture of diastereomers. (Note: even with purification, the spectral data for this product was highly ambiguous and possibly still contained impurities, hence the uncertain yield for this step).

Carboxylic Acid 56. Aldehyde **47** (0.386 g, 0.736 mmol, 1.0 equiv) dissolved in a mixture of THF/t-BuOH (1/1, 30 mL) at 25 °C. Resorcinol (0.810 g, 7.36 mmol, 10 equiv) was then added in a single portion followed sequentially by a solution of NaH_2PO_4 (0.918 g, 5.89 mmol, 8.0 equiv) in water (7 mL) and then by a solution of $NaClO_2$ (0.200 g, 2.21 mmol, 3.0 equiv) in water (7 mL). The resultant mixture was then allowed to stir for 12 h at 25 °C open to air. Upon completion, the reaction contents were quenched with saturated aqueous NH_4Cl (15 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were then washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant

crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3/2 then CH_2Cl_2/MeOH, 9/1) to give pure carboxylic acid **56** (0.339 g, 85% yield) as a pale yellow foam. **56**: R_f = 0.18 (silica gel, hexanes/EtOAc, 1/1); IR (film) νmax 2938, 2839, 2340, 1686, 1508, 1457, 1320, 1205, 1157, 1061, 834; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.33 (m, 5 H), 7.33 (d, *J* = 8.8 Hz, 2 H), 7.08 (d, *J* = 16.0 Hz, 1 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.82 (d, *J* = 16.0 Hz, 1 H), 6.70 (d, *J* = 2.4 Hz, 1 H), 6.46 (d, *J* = 2.4 Hz, 1 H), 6.45 (d, *J* = 2.4 Hz, 2 H), 6.33 (t, *J* = 2.4 Hz, 1 H), 5.30 (s, 1 H), 5.07 (s, 2 H), 3.85 (s, 3 H), 3.77 (s, 3 H), 3.70 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 160.5, 159.8, 158.7, 158.1, 139.8, 139.5, 136.8, 131.9, 130.1, 128.6, 128.0, 127.9, 127.4, 124.4, 118.0, 115.1, 107.6, 1034, 98.8, 98.5, 70.0, 55.6, 55.4, 55.1, 49.0; HRMS (FAB+) calcd for $C_{33}H_{32}O_7^+$ [M+] 540.2148, found 540.2133.

Lactone S1. Carboxylic acid **56** (0.040 g, 0.074 mmol, 1.0 equiv) was dissolved in MeCN (12 mL) at 25 °C and then a solution of IDSI (0.120 g, 0.148 mmol, 2.0 equiv) in MeCN (4 mL) added quickly via syringe. After stirring for 1 min at 25 °C, the reaction contents were quenched with a mixture of 5% aqueous Na_2SO_3/saturated aqueous NaHCO3 (1/1, 5 mL) and the resultant bi-phasic mixture was stirred vigorously for 5 min. The reaction contents were then extracted with CH2Cl2 (3 × 20 mL), and the combined organic extracts were dried (MgSO4), filtered, and concentrated. Carrying this material forward without further purification, the newly formed lactone (**59**) was dissolved in CH_2Cl_2 (5 mL) at 25 °C and BBr_3 (1.9 mL, 1.0 M in CH_2Cl_2, 1.9 mmol, 25 equiv) added via syringe in a single portion. The resultant reaction mixture was then stirred at 25 °C for 24 h. Upon completion, the reaction contents were quenched with water (3 mL), and the resultant bi-phasic system was stirred vigorously for 2 min and extracted with EtOAc (3 × 10 mL). The combined organic extracts were then washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude,

dark red oil was purified by preparative thin-layer chromatography (silica gel, CH_2Cl_2/MeOH, 4/1) to give lactone **S1** (10.5 mg, 36% yield over 2 steps) as a red oil. **S1**: R_f = 0.15 (silica gel, CH_2Cl_2/MeOH, 9/1); IR (film) νmax 3435 (br), 2922, 2851, 1716, 1458, 1376, 1262, 1097, 1025, 802; ^{1}H NMR (400 MHz, acetone-d6) δ 8.62 (s, -OH, 1 H), 8.37 (s, -OH, 1 H), 8.22 (s, -OH, 1 H), 8.04 (s, -OH, 1 H), 7.94 (s, -OH, 1 H), 6.99 (d, *J* = 8.4 Hz, 2 H), 6.72 (d, *J* = 8.8 Hz, 2 H), 6.61 (d, *J* = 2.0 Hz, 1 H), 6.46 (d, *J* = 2.4 Hz, 1 H), 6.37 (d, *J* = 2.0 Hz, 1 H), 6.23 (d, *J* = 2.0 Hz, 1 H), 5.45 (d, *J* = 2.8 Hz, 1 H), 4.89 (s, 1 H), 4.45 (d, *J* = 2.8 Hz, 1 H); ^{13}C NMR (100 MHz, acetone-d6) δ 172.4, 158.5, 158.4, 157.8, 156.6, 153.9, 138.5, 138.1, 134.9, 130.1, 117.2, 115.5, 115.1, 107.7, 105.2, 103.2, 84.8, 48.8, 47.9; HRMS (FAB+) calcd for $C_{22}H_{17}O_7^+$ [M+] 393.0974, found 393.0983.

Perbenzylated Lactone 61. K_2CO_3 (128 mg, 0.926 mmol, 30 equiv), BnBr (110 μL, 0.926 mmol, 30 equiv), and *n*-Bu_4NI (22.9 mg, 0.062 mmol, 2.0 equiv) were added sequentially and in single portions to a solution of lactone **S1** (12.2 mg, 0.031 mmol, 1.0 equiv) in acetone (3 mL) at 25 °C. The resultant reaction mixture was stirred for 12 h at 56 °C. Upon completion, the reaction contents were cooled to 25 °C, quenched with water (2 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) to give lactone **61** (23.2 mg, 89% yield) as a pale yellow oil.

Perbenzylated Hopeahainol D 64. 4-benzyloxybromobenzene (0.156 g, 0.593 mmol, 50 equiv) was dissolved in THF (4 mL) and argon was bubbled through solution for 15 min at 25 °C. Once this operation was complete, the reaction solution was cooled to –78 °C, *n*-BuLi (0.371 mL, 1.6 M in THF, 0.593 mmol, 50 equiv) was added in a single portion, and the reaction

mixture allowed to stir for 15 min at –78 °C. A solution of lactone **61** (10.5 mg, 0.012 mmol, 1.0 equiv) in THF (1 mL) added quickly via syringe at –78 °C, and after stirring the resultant mixture for 20 min at –78 °C, reaction contents were quenched by the addition of water (2 mL) and allowed to warm to 25 °C. The reaction mixture was then extracted with EtOAc (3 × 5 mL), and the combined organic extracts were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) to provide the desired intermediate **62** which was carried forward directly without further purification. Pressing forward, the so- obtained product was dissolved in CH_2Cl_2 (3 mL) and cooled to –78 °C. Et_3SiH (0.095 mL, 0.593 mmol, 50 equiv) and BF_3•OEt_2 (0.015 mL, 0.118 mmol, 10 equiv) were then added sequentially and in single portions at –78 °C, at which time the cold bath was removed and resultant reaction mixture was allowed to stir for 10 min. Upon completion, the reaction contents were quenched by the addition of water (1 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were then washed with water (5 mL) and brine (5 mL), dried (MgSO4), filtered, and concentrated. Purification of the resultant crude yellow oil by preparative thin-layer chromatography (silica gel, hexanes/EtOAc, 5/2) gave perbenzylated hopeahainol D (20, 7.2 mg, 57% yield over 2 steps) as a colorless oil. **64**: R_f = 0.42 (silica gel, hexanes/EtOAc, 3/1); IR (film) νmax 3063, 3032, 2921, 2866, 1604, 1509, 1454, 1377, 1241, 1174, 1144, 1097, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.27 (m, 22 H), 7.19–7.00 (m, 3 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.0 Hz, 2 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 6.64–6.62 (m, 3 H), 6.55 (d, *J* = 2.0 Hz, 1 H), 6.44 (d, *J* = 2.0 Hz, 1 H), 6.34 (d, *J* = 2.0 Hz, 1 H), 5.21 (d, *J* = 2.0 Hz, 1 H), 5.09 (s, 2 H), 5.05–5.04 (m, 3 H), 5.02 (s, 2 H), 4.93 (d, *J* = 11.2 Hz, 1 H), 4.89 (d, *J* = 11.6 Hz, 1 H), 4.75 (d, *J* = 2.4 Hz, 1 H), 4.61 (d, *J* = 11.2 Hz, 1 H), 4.47 (d, *J* = 11.2 Hz, 1 H), 4.32 (d, *J* = 2.0 Hz, 1 H); ^{13C}

NMR (100 MHz, $CDCl_3$) δ 158.8, 158.8, 157.9, 157.5, 157.0, 153.7, 141.5, 139.1, 137.8, 137.5, 137.2, 137.0, 136.9, 136.8, 136.6, 133.2, 129.8, 128.6, 128.6, 128.6, 128.5, 128.1, 128.0, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4, 127.4, 127.2, 123.5, 118.8, 114.0, 103.3, 99.9, 99.1, 82.0, 80.1, 70.4, 70.3, 70.1, 70.0, 69.9, 69.7, 52.6, 44.9; HRMS (FAB+) calcd for $C_{70}H_{58}O_7^+$ [M+] 1010.42, found 1009.23.

Hopeahainol D 3. Perbenzylated hopeahainol D (**64**, 9.0 mg, 0.009 mmol, 1.0 equiv) was dissolved in a mixture of EtOAc/MeOH (1/1, 4 mL) and 10% Pd/C (48 mg, 0.045 mmol, 5 equiv) added at 25 °C. Hydrogen gas was then bubbled through reaction mixture for 20 min, at which time MeOH (2 mL) was added and the reaction mixture was allowed to stir overnight at 25 °C under a positive pressure of hydrogen from a standard balloon. Upon completion, the reaction mixture was filtered directly though Celite, washed with EtOAc (2 × 5 mL) and MeOH (3 × 5 mL), concentrated, and purified by preparative thin-layer chromatography (silica gel, CH_2Cl_2/MeOH, 4/1) to give hopeahainol D (**3**, 3.3 mg, 79% yield) as a colorless oil. **3**: R_f = 0.45 (silica gel, CH_2Cl_2/MeOH, 4/1); IR (film) νmax 3386 (br), 2923, 2852, 1735, 1461, 1073, 715; ^{1}H NMR (400 MHz, DMSO-d6) δ 9.27 (s, -OH, 1 H), 9.18 (s, -OH, 1 H), 9.14 (s, -OH, 1 H), 8.98 (s, -OH, 1 H), 8.86 (s, -OH, 1 H), 8.59 (s, -OH, 1 H), 7.12 (d, *J* = 8.4 Hz, 2 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 6.60 (d, *J* = 8.4 Hz, 2 H), 6.56 (d, *J* = 8.4 Hz, 2 H), 6.32 (d, *J* = 1.6 Hz, 1 H), 6.20 (d, *J* = 2.0 Hz, 1 H), 5.94 (d, *J* = 2.4 Hz, 1 H), 5.92 (d, *J* = 2.0 Hz, 1 H), 4.95 (d, *J* = 1.6 Hz, 1 H), 4.72 (s, 1 H), 4.35 (d, *J* = 2.4 Hz, 1 H), 3.95 (d, *J* = 1.2 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-d6) δ 157.1, 156.5, 155.7, 155.5, 154.8, 151.9, 141.5, 139.1, 135.6, 131.6, 129.4, 127.4, 119.6, 114.3, 114.1, 113.7, 108.5, 103.5, 101.3, 101.0, 81.2, 80.0, 52.0, 44.5; LRMS (FAB-) calcd for $C_{28}H_{21}O7^-$ [M – H]- 469.1, found 469.0. These spectral data match that originally reported by Ge and co-workers, a summary of which is found in Table S1 at the end of this experimental section.

Heimiol A 2. Hopeahainol D (**3**, 0.5 mg, 0.005 mmol, 1.0 equiv) was dissolved in MeOH (2 mL) at 25 °C and then BF_3•OEt_2 (5.0 μL, 0.040 mmol, 8.0 equiv) and BCl_3 (10 μL, 1.0 M in CH2Cl2, 0.01 mmol, 2.0 equiv) were added sequentially and in single portions. The resultant reaction mixture was stirred for 2.5 h at 25 °C. Upon completion, reaction contents were concentrated directly, redissolved in EtOAc (5 mL), poured into saturated aqueous NH_4Cl, and extracted with EtOAc (3 × 5 mL). The combined organic extracts were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to give heimiol A (1, 0.5 mg, quantitative yield) as a pale yellow oil. This reaction was repeated several times. [Note: at the above reported scale and concentration, this transformation is highly reproducible; however, attempts to increase the scale to 2–3 mg resulted in mixtures of starting material and product.] **1:** R_f = 0.45 (silica gel, CH_2Cl_2/MeOH, 4/1); IR (film) νmax 3330 (br), 2957, 1678, 1611, 1512, 1457, 1332, 1200, 1142, 1079, 1041, 834; ^{1}H NMR (400 MHz, acetone-d6) δ 8.07 (s, -OH, 1 H), 8.06 (s, -OH, 1 H), 7.99 (s, -OH, 1 H), 7.96 (s, -OH, 1 H), 7.94 (s, -OH, 1 H), 7.47 (s, -OH, 1 H), 7.16 (d, *J* = 8.8 Hz, 2 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 6.73 (d, *J* = 8.4 Hz, 2 H), 6.62 (d, *J* = 8.8 Hz, 2 H), 6.49 (d, *J* = 2.4 Hz, 1 H), 6.41 (d, *J* = 2.8 Hz, 1 H), 6.23 (d, *J* = 1.6 Hz, 1 H), 6.17 (d, *J* = 2.4 Hz, 1 H), 5.58 (s, 1 H), 4.98 (d, *J* = 3.2 Hz, 1 H), 4.33 (d, *J* = 3.2 Hz, 1 H), 4.25 (s, 1 H); ^{13}C NMR (100 MHz, acetone-d6) δ 158.1, 157.4, 157.1, 157.0, 156.1, 154.6, 147.4, 142.6, 137.0, 136.9, 130.0, 127.9, 116.8, 116.2, 115.3, 115.2, 107.3, 104.7, 102.2, 102.0, 81.5, 81.4, 50.9, 46.9; LRMS calcd for $C_{28}H_{22}O_7^+$ [M]+ 470.14, found 470.60. These spectral data match that originally reported by Weber and co-workers, a summary of which is found in Table S2 at the end of this experimental section. [Important Note: The discrepancy among the two C13 peaks is also noted in a subsequent isolation of heimiol A by Atun and co-workers, one which indicates that the original isolation paper has a typographical error for this one peak; our data is

in complete agreement with that of the Atun group.]

Yuccaone A Core 69. To a solution of aldehyde **47** (50.0 mg, 0.112 mmol, 1.0 equiv) in a mixture of acetone (6 mL) and water (2 mL) at 25 °C was added solid NMO (39.0 mg, 0.335 mmol, 3.0 equiv) and OsO_4 (0.10 mL, 2.5% in *t*-BuOH, 0.011 mmol, 0.1 equiv), and the resultant reaction mixture was stirred for 2 h at 25 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous Na_2SO_3 (3 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to give the desired diol intermediate **66** which was carried forward directly without any further purification. Next, this newly formed material was dissolved in toluene (3 mL) and $Ph_3P(OEt)_2$ (0.3 mL, 1.0 M in toluene, 0.3 mmol, 3.0 equiv) was added via syringe at 25 °C. The resultant reaction mixture was then heated at 70 °C for 36 h. Upon completion, the reaction contents were cooled to 25 °C, concentrated, and purified directly by preparative thin-layer chromatography (silica gel, $CHCl_3/Et_2O$, 9/1) to give yuccaone A core **69** (11.2 mg, 22% over 2 steps) as a colorless oil. **69**: R_f = 0.43 (silica gel, hexanes/EtOAc, 1/1); IR (film) ν_{max} 3415 (br), 3002, 2937, 2838, 1717, 1606, 1514, 1460, 1250, 1205, 1152, 1042, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1 H), 6.78 (d, *J* = 8.8 Hz, 2 H), 6.72 (d, *J* = 2.0 Hz, 1 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 6.44 (d, *J* = 2.0 Hz, 1 H), 6.27 (t, *J* = 2.0 Hz, 1 H), 5.50 (d, *J* = 2.0 Hz, 2 H), 5.29 (dd, *J* = 9.2, 7.2 Hz, 1 H), 4.28 (d, *J* = 9.2 Hz, 1 H), 3.88 (s, 3 H), 3.74 (s, 3 H), 3.68 (s, 3 H), 3.48 (s, 3 H), 2.01 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 162.5, 160.3, 158.8, 156.2, 147.1, 139.1, 130.9, 128.8, 120.5, 113.4, 107.1, 99.8, 99.3, 99.3, 78.0, 69.2, 60.4, 55.7, 55.5, 55.3, 55.1; HRMS (FAB+) calcd for $C_{27}H_{28}O_7^+$ [M^+] 464.1835, found 464.1826.

Lactol 72. Lactone **71** (12.0 mg, 0.026 mmol, 1.0 equiv) was dissolved in toluene (2 mL), cooled to –78 °C, and DIBAL-H (0.052 mL, 1.0 M in toluene, 0.052 mmol, 2.0 equiv) was added dropwise. The resultant solution was stirred for 10 min at –78 °C, and which time the cold bath was removed and reaction mixture was allowed to warm to 25 °C over the course of 5 min. Upon completion, the reaction contents were quenched by the slow and careful addition of MeOH (1 mL), diluted with EtOAc (2 mL), and then saturated aqueous sodium potassium tartrate (5 mL) was added and the resultant bi-phasic system was stirred vigorously for 20 min. The reaction contents were then extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to give lactol **72** (11.0 mg, 92%) as a colorless oil.

Permethylated Heimiol A 74. $AlCl_3$ (6.0 mg, 0.043 mmol, 2.0 equiv) was dissolved in anisole (3 mL) and cooled to –30 °C. A solution of lactol **72** (10.0 mg, 0.022 mmol, 1.0 equiv) in anisole (1.5 mL) was then added quickly. After stirring the resultant solution for 2 min at –30 °C, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (2 mL), warmed to 25 °C, and extracted with EtOAc (3 × 5 mL). The combined organic extracts were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude pale yellow oil purified by preparative thin-layer chromatography (silica gel, $CHCl_3/Et_2O$, 19/1) to give permethylated heimiol A (**74**, 10.0 mg, 84% yield) as a white foam. **74**: R_f = 0.70 (silica gel, hexanes/EtOAc, 1/1); IR (film) ν_{max} 2998, 2935, 2836, 1606, 1510, 1461, 1299, 1246, 1173, 1144, 1095; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.4 Hz, 2 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 6.53 (d, *J* = 2.4 Hz, 1 H), 6.48 (d, *J* = 2.4 Hz, 1 H), 6.31 (d, *J* = 2.4 Hz, 1 H), 6.25 (d, *J* =2.8 Hz, 1 H), 5.66 (s, 1 H), 5.07 (d, *J* = 3.2 Hz, 1 H), 4.37 (d, *J* = 3.2 Hz, 1 H), 4.31 (s, 1 H), 3.82 (s, 1 H), 3.81 (s, 1 H), 3.78

(s, 1 H), 3.72 (s, 1 H), 3.62 (s, 1 H), 3.39 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 159.3, 159.0, 158.5, 157.6, 156.3, 145.5, 140.8, 137.2, 136.3, 128.7, 127.1, 118.9, 118.6, 113.3, 113.1, 104.7, 101.9, 98.0, 97.5, 80.7, 80.6, 55.8, 55.5, 55.4, 55.3, 55.2, 55.1, 50.0, 45.9; HRMS (FAB+) calcd for $C_{34}H_{35}O_7^+$ $[M + H]^+$ 555.2383, found 555.2387.

Permethylated Symmetric Dimer 75. $AlCl_3$ (5.0 mg, 0.036 mmol, 2.0 equiv) was dissolved in a mixture of CH_2Cl_2 (4 mL) and anisole (0.5 mL). Lactol **72** (8.4 mg, 0.018 mmol, 1.0 equiv) was then added quickly as a solution in CH_2Cl_2 (1.5 mL) at 25 °C. After stirring the resulting reaction mixture for 1 min at 25 °C, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (2 mL), stirred vigorously for an additional 3 min at 25 °C, and extracted with EtOAc (3 × 5 mL). The combined organic extracts were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude pale yellow oil was purified by preparative thin-layer chromatography (silica gel, $CHCl_3/Et_2O$, 19/1) to give permethylated symmetric dimer **75** (9.2 mg, 92% yield) as a colorless oil. **75**: R_f = 0.70 (silica gel, hexanes/EtOAc, 1/1); IR (film) ν_{max} 2934, 1608, 1527, 1351, 1246, 1203, 1042, 804, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.4 Hz, 4 H), 6.79 (d, J = 8.8 Hz, 4 H), 6.43 (d, J = 2.4 Hz, 2 H), 6.23 (d, J = 2.4 Hz, 2 H), 5.07 (s, 2 H), 4.06 (s, 2 H), 3.83 (s, 6 H), 3.76 (s, 6 H), 3.54 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 158.3, 157.9, 139.0, 137.0, 129.2, 115.8, 113.3, 100.8, 97.4, 76.6, 55.3, 55.2, 45.6; HRMS (FAB+) calcd for $C_{34}H_{34}O_7^+$ $[M^+]$ 554.2305, found 554.2291.

Symmetric Dimer S2. Permethylated symmetric dimer **75** (7.3 mg, 0.013 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (3 mL) and then BBr_3 (0.4 mL, 1.0 M in CH_2Cl_2, 0.4 mmol, 30 equiv) was added in a single portion at 25 °C. The resulting dark red-brown reaction mixture stirred for 24 h at 25 °C. Upon completion, the reaction contents were quenched by the addition

of water (2 mL), stirred vigorously for an additional 2 min at 25 °C, and extracted with EtOAc (3 × 7 mL). The combined organic extracts were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to yield symmetric dimer **S2** (6.2 mg, 99% yield) as an orange oil. **S2**: R_f = 0.08 (silica gel, CH_2Cl_2/MeOH, 9/1); IR (film) ν_{max} 3326 (br), 2955, 2920, 2851, 1612, 1512, 1460, 1259, 1173, 1132, 1038, 828; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.00 (s, -OH, 2 H), 7.93 (s, -OH, 2 H), 7.79 (s, -OH, 2 H), 7.11 (d, J = 8.4 Hz, 4 H), 6.70 (d, J = 8.4 Hz, 4 H), 6.44 (d, J = 2.0 Hz, 2 H), 6.19 (d, J = 2.0 Hz, 2 H), 4.94 (s, 2 H), 4.06 (s, 2 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 157.3, 156.7, 156.3, 140.9, 137.0, 130.4, 115.3, 114.1, 103.9, 102.4, 77.7, 46.7; HRMS (FAB+) calcd for $C_{28}H_{22}O_7^+$ [M^+] 470.1366, found 470.1361.

Ampelopsin F Core 83. Me_3SI (1.20 g, 5.88 mmol, 10 equiv) was added to THF (30 mL) at 0 °C, and then *n*-BuL*i* (3.30 mL, 1.6 M in hexanes, 5.29 mmol, 9.0 equiv) was added in a single portion and the resulting pale yellow solution was stirred for 2 min at 0 °C. A solution of ketone **33** (0.300 g, 0.588 mmol, 1.0 equiv) in THF (20 mL) was then added over the course of 10 min, and the resulting mixture was allowed to stir for an additional 1 h at 0 °C. Upon completion, the reaction contents were quenched by the addition of water (20 mL) and extracted with EtOAc (3 × 40 mL). The combined organic extracts were then washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated to afford the desired epoxide intermediate **80**. [Note: This material is not very stable and must be carried forward without delay for optimal results.] Next, this newly formed intermediate was immediately dissolved in benzene (20 mL) at 25 °C and solid ZnI_2 (0.188 g, 0.588 mmol, 1.0 equiv) was added in a single portion. After stirring the resultant mixture for 2 h at 25 °C open to air, the reaction contents were quenched with water (10 mL), stirred vigorously for 3 min at 25 °C, and extracted with EtOAc (3 × 20 mL). The combined organic extracts were then washed with water (15 mL) and

brine (15 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude orange oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 4/1) to give ampelopsin F core **83** (0.195 g, 63% yield over 2 steps) as a white foam. **83**: R_f = 0.38 (silica gel, hexanes/EtOAc, 1/1); IR (film) νmax 3456 (br), 2936, 2837, 1717, 1603, 1456, 1319, 1206, 1140, 833; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.30 (m, 5 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 6.63 (d, *J* = 2.0 Hz, 1 H), 6.45 (d, *J* = 2.0 Hz, 1 H), 6.24 (d, *J* = 2.0 Hz, 1 H), 6.22 (d, *J* = 2.4 Hz, 1 H), 5.04 (s, 2 H), 4.59 (s, 1 H), 4.19 (d, *J* = 1.2 Hz, 1 H), 4.04 (s, 1 H), 3.81 (s, 1 H), 3.79 (s, 1 H), 3.78 (s, 1 H), 3.39 (s, 1 H), 3.26 (s, 1 H), 1.69 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 159.2, 159.1, 156.8, 156.1, 144.2, 143.8, 138.9, 137.2, 128.6, 128.5, 127.9, 127.9, 127.5, 115.1, 114.3, 103.2, 102.3, 97.5, 97.2, 70.0, 58.3, 55.5, 55.3, 55.3, 55.2, 50.9, 46.1; HRMS (FAB+) calcd for $C_{33}H_{32}O_6^+$ [M+] 524.2199, found 524.2209.

Ketone 84. A solution of DMSO (0.054 mL, 0.762 mmol, 10 equiv) in CH_2Cl_2 (1 mL) was added to solution of oxalyl chloride (0.033 mL, 0.381 mmol, 5.0 equiv) in CH_2Cl_2 (1.5 mL) at –78 °C, and the resultant mixture was stirred for 20 min at –78 °C. The reaction mixture was then warmed to –30 °C over the course of 5 min, and alcohol **83** (40.0 mg, 0.076 mmol, 1.0 equiv) added as a solution in CH_2Cl_2 (1.5 mL). After the resultant mixture was stirred for 30 min at –30 °C, Et_3N (0.160 mL, 1.14 mmol, 15 equiv) was added, the cold bath was removed, and the reaction contents were left to stir for 10 min as they warmed to 25 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3/1) to give ketone **84** (32.0 mg, 80% yield) as a white solid.

Hindered Aryl Alcohol 85. Ketone **84** (67.0 mg, 0.128 mmol, 1.0 equiv) was dissolved in THF (6 mL) at 25 °C, and 4-methoxyphenylmagnesium bromide (1.30 mL, 1.0 M in THF, 1.3 mmol, 10 equiv) was added in a single portion and the resultant mixture was stirred at 25 °C for 10 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (3 mL) and extracted with EtOAc (3 × 8 mL). The combined organic extracts were then washed with water (8 mL) and brine (8 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3/1) to give hindered aryl alcohol **85** (67.0 mg, 83% yield) as a white solid. **85**: R_f = 0.75 (silica gel, hexanes/EtOAc, 1/1); IR (film) νmax 3462 (br), 2925, 2851, 1605, 1510, 1461, 1317, 1248, 1204, 1176, 1143, 1038, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.31 (m, 5 H), 7.28 (d, *J* = 8.8 Hz, 2 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 6.70 (d, *J* = 8.8 Hz, 2 H), 6.62 (d, *J* = 2.0 Hz, 1 H), 6.55 (d, *J* = 2.0 Hz, 1 H), 6.33 (d, *J* = 2.4 Hz, 1 H), 6.11 (d, 2.0 Hz, 1 H), 5.03 (s, 2 H), 4.30 (s, 2 H), 3.86 (s, 3 H), 3.84 (s, 1 H), 3.75 (s, 3 H), 3.70 (s, 3 H), 3.68 (s, 3 H), 3.48 (s, 3 H), 2.06 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.4, 159.2, 158.3, 156.6, 154.5, 146.1, 143.0, 137.8, 137.3, 137.2, 129.3, 128.5, 127.9, 127.8, 127.7, 127.6, 115.0, 114.2, 113.4, 104.9, 100.5, 97.1, 96.9, 83.0, 70.0, 56.6, 55.4, 55.3, 55.2, 55.1, 55.0, 53.4, 45.0; HRMS (FAB+) calcd for $C_{40}H_{38}O_7^+$ [M+] 630.2618, found 630.2629.

Protected Analog 87. Alcohol **85** (12.0 mg, 0.020 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2 mL), cooled to –78 °C, and then Et_3SiH (0.090 mL, 0.586 mmol, 30 equiv) and BF_3•OEt_2 (0.025 mL, 0.195 mmol, 10 equiv) were added sequentially. The resultant reaction mixture was stirred for 5 min at –78 °C. Upon completion, the reaction contents were quenched by the addition of water (1 mL), allowed to warm to 25 °C, and extracted with EtOAc (3 × 5 mL). The combined organic extracts were then washed with water (5 mL) and brine (5 mL),

dried ($MgSO_4$), filtered, and concentrated to give permethylated analog **87** (12.0 mg, 99% yield) as a white solid.

Ampelopsin F Analog 89. **87** (6.0 mg, 0.010 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2 mL) and BBr_3 (0.30 mL, 1.0 M in CH2Cl2, 0.300 mmol, 30 equiv) was added in a single portion at 25 °C. The resultant red-brown solution was stirred for 24 h at 25 °C. Upon completion, the reaction contents were quenched by the addition of water (2 mL), stirred vigorously for 3 min at 25 °C, and extracted with EtOAc (3 × 5 mL). The combined organic extracts were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude material was purified by preparative thin-layer chromatography (silica gel, CH_2Cl_2/MeOH, 4/1) to give ampelopsin F analog **89** (3.3 mg, 74% yield) as a colorless oil. **89**: R_f = 0.28 (silica gel, CH_2Cl_2/MeOH, 9/1); IR (film) νmax 3309 (br), 2934, 1602, 1512, 1458, 1329, 1242, 1200, 113, 1133, 830; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.92 (s, -OH, 1 H), 8.91 (s, -OH, 1 H), 8.86 (s, -OH, 1 H), 8.81 (s, -OH, 1 H), 8.64 (s, -OH, 1 H), 8.38 (s, -OH, 1 H), 6.56 (d, *J* = 8.4 Hz, 2 H), 6.40 (d, *J* = 2.0 Hz, 1 H), 6.36 (d, *J* = 2.0 Hz, 1 H), 6.23 (d, *J* = 8.4 Hz, 2 H), 6.23 (d, *J* = 8.4 Hz, 2 H), 6.17 (d, *J* = 8.4 Hz, 2 H), 5.96 (d, *J* = 2.0 Hz, 1 H), 5.94 (d, *J* = 2.4 Hz, 1 H), 4.13 (d, *J* = 3.6 Hz, 1 H), 3.69 (d, *J* = 4.4 Hz, 1 H), 3.62 (s, 1 H), 3.46 (t, *J* = 4.0 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-d6) δ 156.8, 156.6, 156.0, 154.4, 154.0, 151.1, 149.7, 143.3, 134.4, 130.0, 129.1, 128.5, 127.6, 113.7, 113.2, 111.3, 105.2, 102.1, 100.3, 52.3, 50.1, 43.0, 42.8; HRMS (FAB+) calcd for $C_{28}H_{22}O_6^+$ [M+] 454.1416, found 454.1416.

Permethylated Gnetuhainin C Analog 88. Ketone **84** (0.150 g, 0.336 mmol, 1.0 equiv) was dissolved in THF (10 mL) at 25 °C, and 2,4- dimethoxyphenylmagnesium bromide (2.00 mL, 0.5 M in THF, 1.0 mmol, 3.0 equiv) was added in a single portion and the resultant mixture was stirred at 25 °C for 10 min. Upon completion, the reaction contents were quenched by the

addition of saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were then washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3/1) to give the desired tetraaryl alcohol **86** (0.196 g, 99% yield) as an orange foam. Next, a portion of this alcohol (0.178 g, 0.304 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (10 mL), cooled to –78 °C, and then Et_3SiH (1.40 mL, 9.12 mmol, 30 equiv) and BF_3•OEt_2 (0.386 mL, 3.04 mmol, 10 equiv) were added sequentially. The resultant reaction mixture was stirred for 5 min at –78 °C. Upon completion, the reaction contents were quenched by the addition of water (5 mL), allowed to warm to 25 °C, and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexanes/EtOAc, 2/1) to give permethylated analog **88** (0.146 g, 84% yield) as a white crystalline solid. **88**: R_f = 0.63 (silica gel, hexanes/EtOAc, 1/1); IR (film) νmax 2996, 2949, 2834, 1606, 1508, 1463, 1313, 1208, 1137, 1040, 823; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.4 Hz, 1 H), 6.68 (d, *J* = 2.4 Hz, 1 H), 6.67 (d, *J* = 2.0 Hz, 1 H), 6.36 (br m, 4 H), 6.22 (d, *J* = 2.4 Hz, 1H), 6.21 (d, *J* = 2.8 Hz, 1 H), 6.17 (dd, *J* = 8.4, 2.4 Hz, 1 H), 5.76 (d, *J* = 2.4 Hz, 1 H), 4.34 (d, *J* = 3.6 Hz, 1 H), 4.26 (d, *J* = 3.6 Hz, 1 H), 3.92 (d, *J* = 1.2 Hz, 1 H), 3.88 (s, 3 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.69 (s, 3 H), 3.69 (s, 3 H), 3.66 (t, *J* = 4.0 Hz, 1 H), 3.36 (s, 3 H), 3.31 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 159.4, 159.2, 159.1, 159.0, 156.0, 153.8, 149.4, 143.9, 135.4, 130.9, 129.4, 128.7, 121.2, 114.8, 11.7, 103.9, 102.9, 101.0, 97.2, 96.6, 96.2, 55.5, 55.4, 55.3, 55.2, 55.2, 54.9, 54.2, 50.2, 47.7, 45.4, 42.5; HRMS (FAB+) calcd for $C_{35}H_{36}O_7^+$ [M+] 568.2461, found 568.2462.

Gnetuhainin C Analog 90. BBr_3 (1.76 mL, 1.0 M in CH_2Cl_2, 1.76 mmol, 50 equiv) was

added in a single portion at 25 °C to **88** (20.0 mg, 0.0352 mmol, 1.0 equiv). The resultant red-brown solution was stirred in a sealed tube for 7 d at 50 °C. Upon completion, the reaction contents were quenched by the addition of water (2 mL), stirred vigorously for 3 min at 25 °C, and extracted with EtOAc (3 × 5 mL). The combined organic extracts were then washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude material was purified by preparative thin-layer chromatography (silica gel, CH_2Cl_2/MeOH, 4/1) to give **90** (13.5 mg, 82% yield) as a colorless oil. **90**: R_f = 0.60 (silica gel, CH_2Cl_2/MeOH, 4/1); IR (film) νmax 3361 (br), 2921, 2851, 1650, 1607, 1508, 1459, 1260, 1206, 1127, 1041, 799; ^{1}H NMR (400 MHz, acetone-d6) δ 7.98 (s, -OH, 1 H), 7.91 (s, -OH, 1 H), 7.86 (s, -OH, 1 H), 7.75 (s, -OH, 1 H), 7.68 (s, -OH, 1 H), 7.57 (s, -OH, 1 H), 6.93 (d, *J* = 8.4 Hz, 1 H), 6.66 (s, -OH), 6.62 (d, *J* = 2.4 Hz, 1 H), 6.55 (d, *J* = 2.0 Hz, 1 H), 6.47 (d, *J* = 7.6 Hz, 2 H), 6.29 (d, *J* = 8.4 Hz, 2 H), 6.09 (d, *J* = 1.6 Hz, 1 H), 6.09 (d, *J* = 2.0 Hz, 1 H), 6.04 (dd, *J* = 8.4, 2.4 Hz, 1 H), 5.84 (d, *J* = 2.4 Hz, 1 H), 4.29 (d, *J* = 3.6 Hz, 1 H), 4.19 (d, *J* = 4.4 Hz, 1 H), 3.85 (s, 1 H), 3.61 (t, *J* = 4.0 Hz, 1 H); ^{13}C NMR (100 MHz, acetone-d6) δ 158.1, 157.9, 157.7, 157.5, 157.2, 154.8, 152.0, 151.7, 145.3, 134.5, 130.5, 130.3, 128.8, 119.2, 114.3, 113.0, 106.7, 105.8, 103.6, 102.7, 101.6, 101.2, 51.2, 48.4, 45.9, 44.4; HRMS (FAB+) calcd for $C_{28}H_{22}O_7^+$ [M+] 470.1366, found 470.1372.

Figure 3. Additional Compounds.

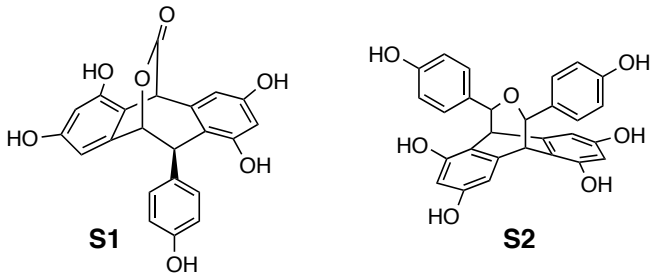


Table 1. NMR Spectral Data Comparison of Natural and Synthetic Hopeahainol D (**2**) in DMSO-d_6; Coupling Constants (J) in Hz.

^{1}H		^{13}C*	
Synthetic Hopeahainol D	**Natural Hopeahainol D**	**Synthetic Hopeahainol D**	**Natural Hopeahainol D**
7.12 (d, J = 8.4 Hz)	7.14 (d, J = 8.4 Hz)	158.4	158.4
6.83 (d, J = 8.4 Hz)	6.85 (d, J = 8.2 Hz)	157.8	157.8
6.60 (d, J = 8.4 Hz)	6.61 (d, J = 8.4 Hz)	157.0	157.0
6.56 (d, J = 8.4 Hz)	6.58 (d, J = 8.2 Hz)	156.8	156.8
6.32 (d, J = 1.6 Hz)	6.33 (d, J = 1.2 Hz)	156.1	156.1
6.20 (d, J = 2.0 Hz)	6.21 (d, J = 1.2 Hz)	153.2	153.1
5.94 (d, J = 2.4 Hz)	5.96 (br s)	142.8	142.8
5.92 (d, J = 2.0 Hz)	5.94 (br s)	140.4	140.4
4.95 (d, J = 1.6 Hz)	4.96 (d, J = 1.4 Hz)	136.9	136.9
4.72 (s)	4.73 (br s)	132.9	132.9
4.35 (d, J = 2.4 Hz)	4.37 (br s)	130.7	130.7
3.95 (d, J = 1.2 Hz)	3.97 (d, J = 1.4 Hz)	128.7	128.7
		120.9	121.0
		115.6	115.6
		115.4	115.4
		115.0	115.0
		109.8	109.8
		104.8	104.8
		102.6	102.7
		102.3	102.4
		82.5	82.5
		81.3	81.4
		53.3	53.3
		45.8	45.8

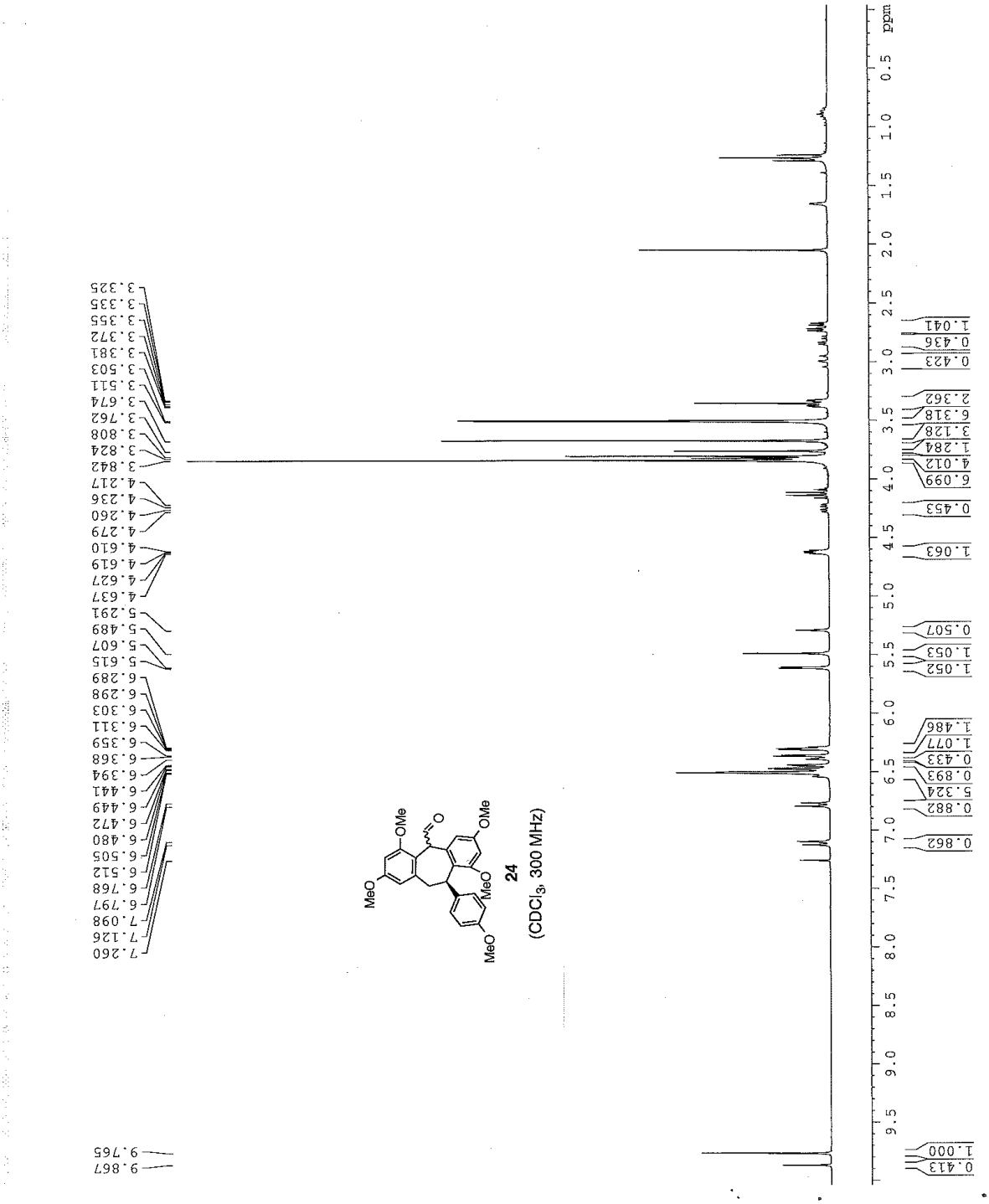
*Note: Observed ^{13}C values are 1.3ppm lower than reported as they were not referenced to the same solvent ppm.

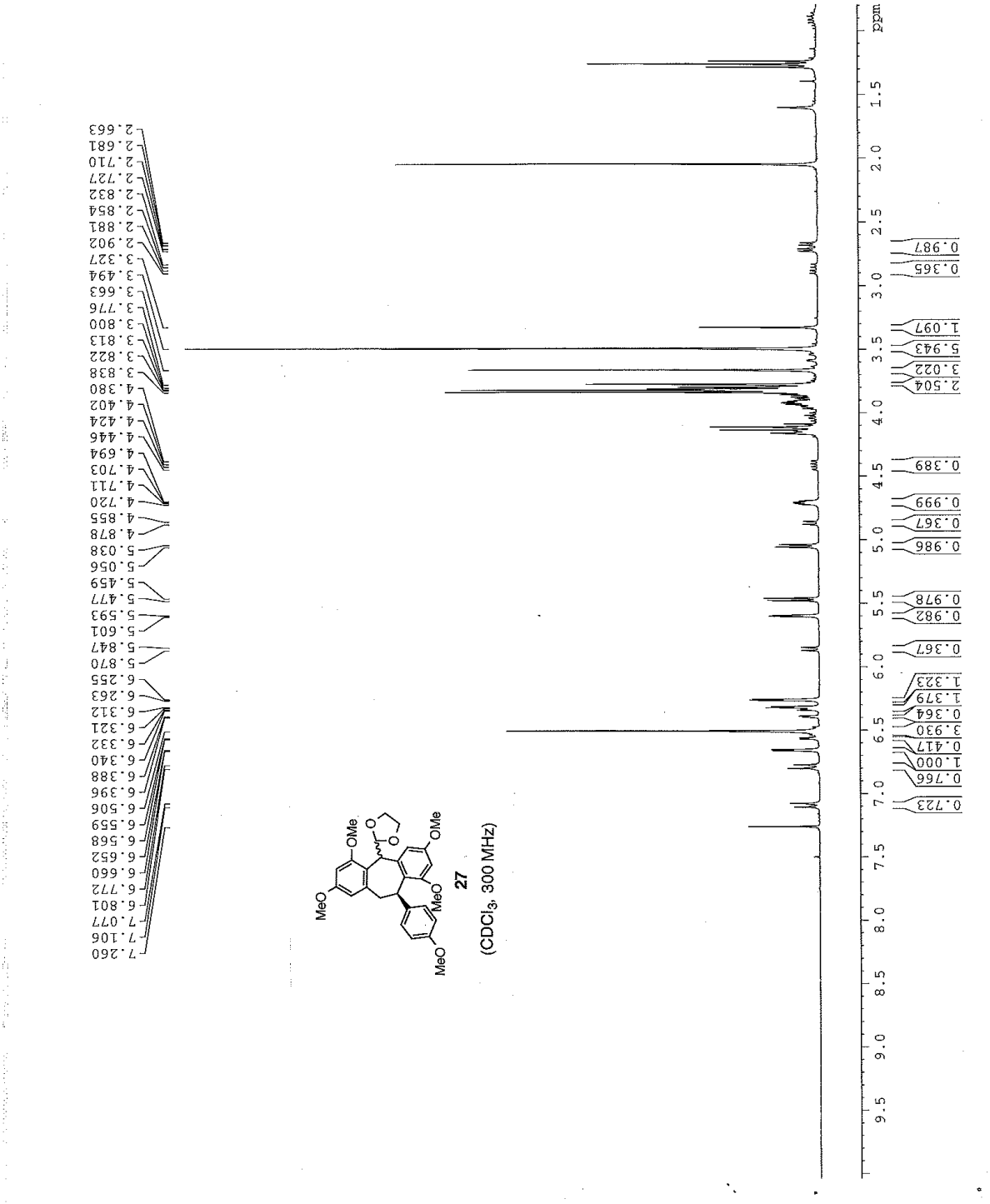
Table 2. NMR Spectral Data Comparison of Natural and Synthetic Heimiol A (**2**) in DMSO-d_6; Coupling Constants (*J*) in Hz.

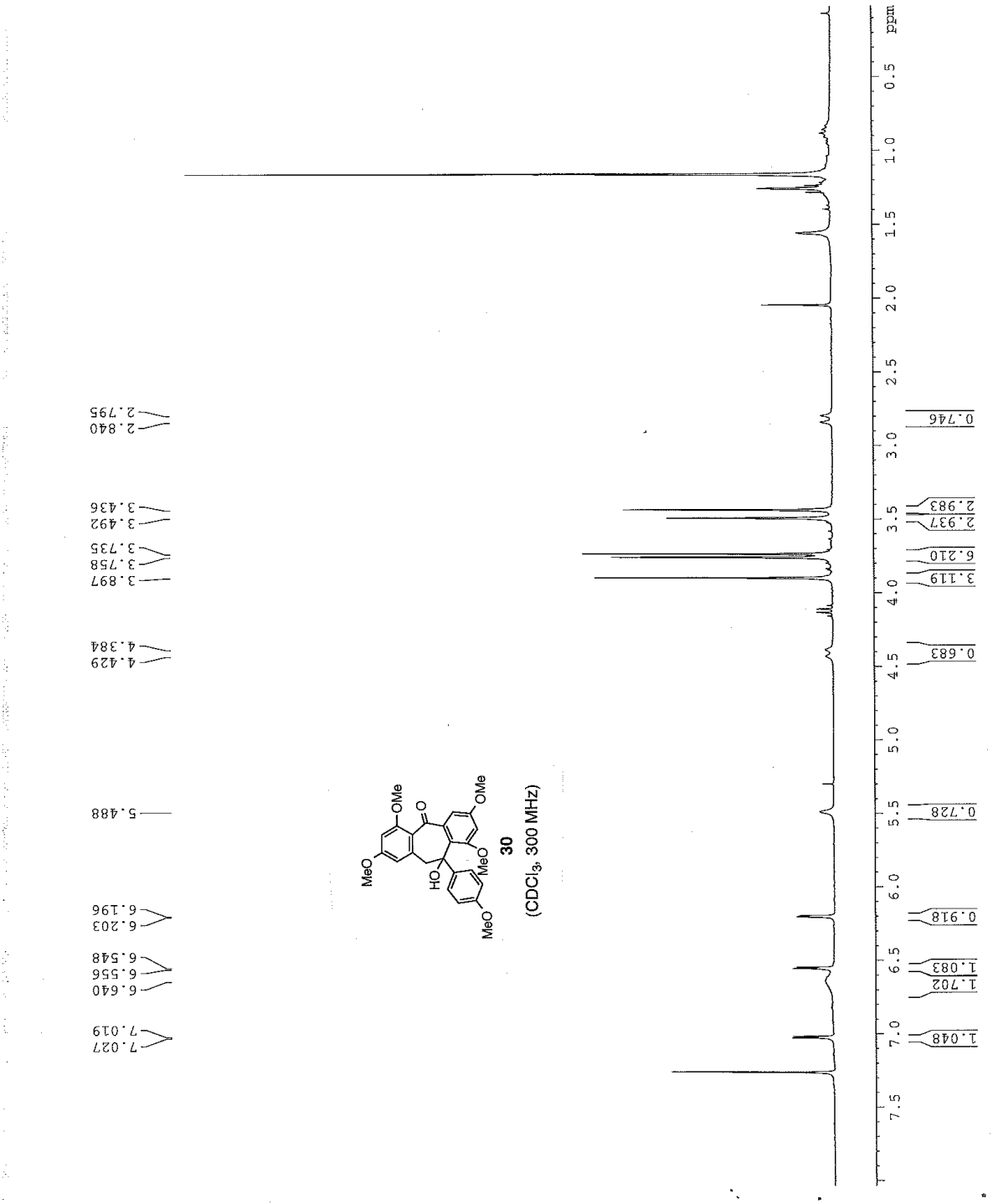
^{1}H		^{13}C	
Synthetic Heimiol A	**Natural Heimiol A**	**Synthetic Heimiol A**	**Natural Heimiol A**
7.16 (d, J = 8.8 Hz)	7.14 (d, J = 8.4 Hz)	158.1	158.0
6.91 (d, J = 8.8 Hz)	6.90 (d, J = 8.5 Hz)	157.4	157.3
6.73 (d, J = 8.4 Hz)	6.71 (d, J = 8.4 Hz)	157.1	157.1
6.62 (d, J = 8.8 Hz)	6.60 (d, J = 8.5 Hz)	157.0	156.9
6.49 (d, J = 2.4 Hz)	6.47 (d, J = 2.1 Hz)	156.1	156.1
6.41 (d, J = 2.8 Hz)	6.40 (d, J = 2.4 Hz)	154.6	154.5
6.23 (d, J = 1.6 Hz)	6.23 (d, J = 2.1 Hz)	147.4	147.4
6.17 (d, J = 2.4 Hz)	6.16 (d, J = 2.4 Hz)	142.6	142.6
5.58 (s)	5.57 (s)	137.0	136.9
4.98 (d, J = 3.2 Hz)	4.96 (d, J = 3.3 Hz)	136.9	136.8
4.33 (d, J = 3.2 Hz)	4.32 (d, J = 3.3 Hz)	130.0	160.1**
4.25 (s)	4.23 (s)	127.9	127.8
		116.8	116.7
		116.2	116.1
		115.3	115.2
		115.2	115.1
		107.3	107.2
		104.7	104.6
		102.2	126.0**
		102.0	101.9
		81.5	81.5
		81.4	81.4
		50.9	50.8
		46.9	46.8

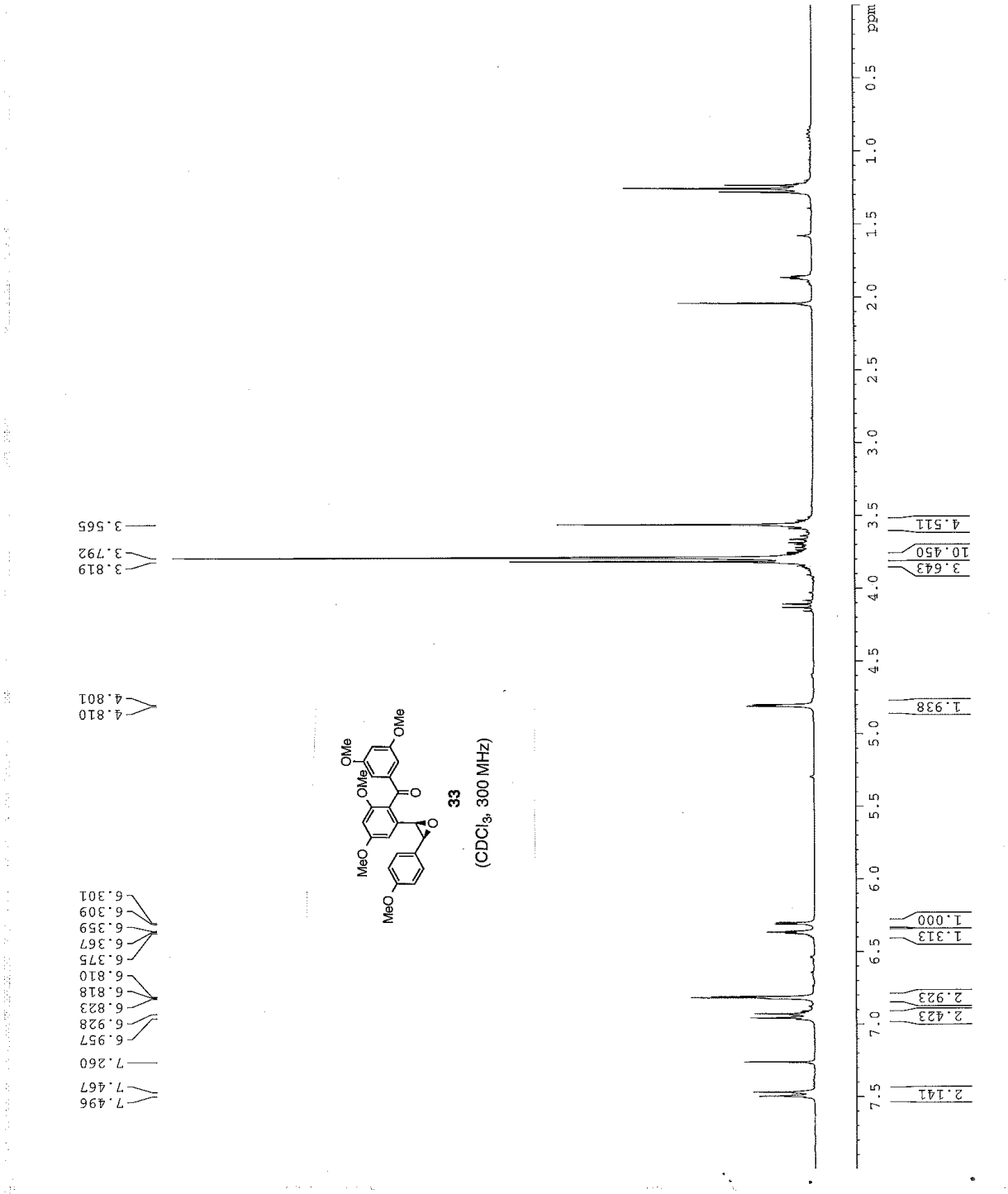
**Note: The same discrepancies observed in these two ^{13}C NMR peaks were also observed in later isolations of heimiol A. They are assumed to be misassigned by the original isolation chemists. For subsequent isolations see:

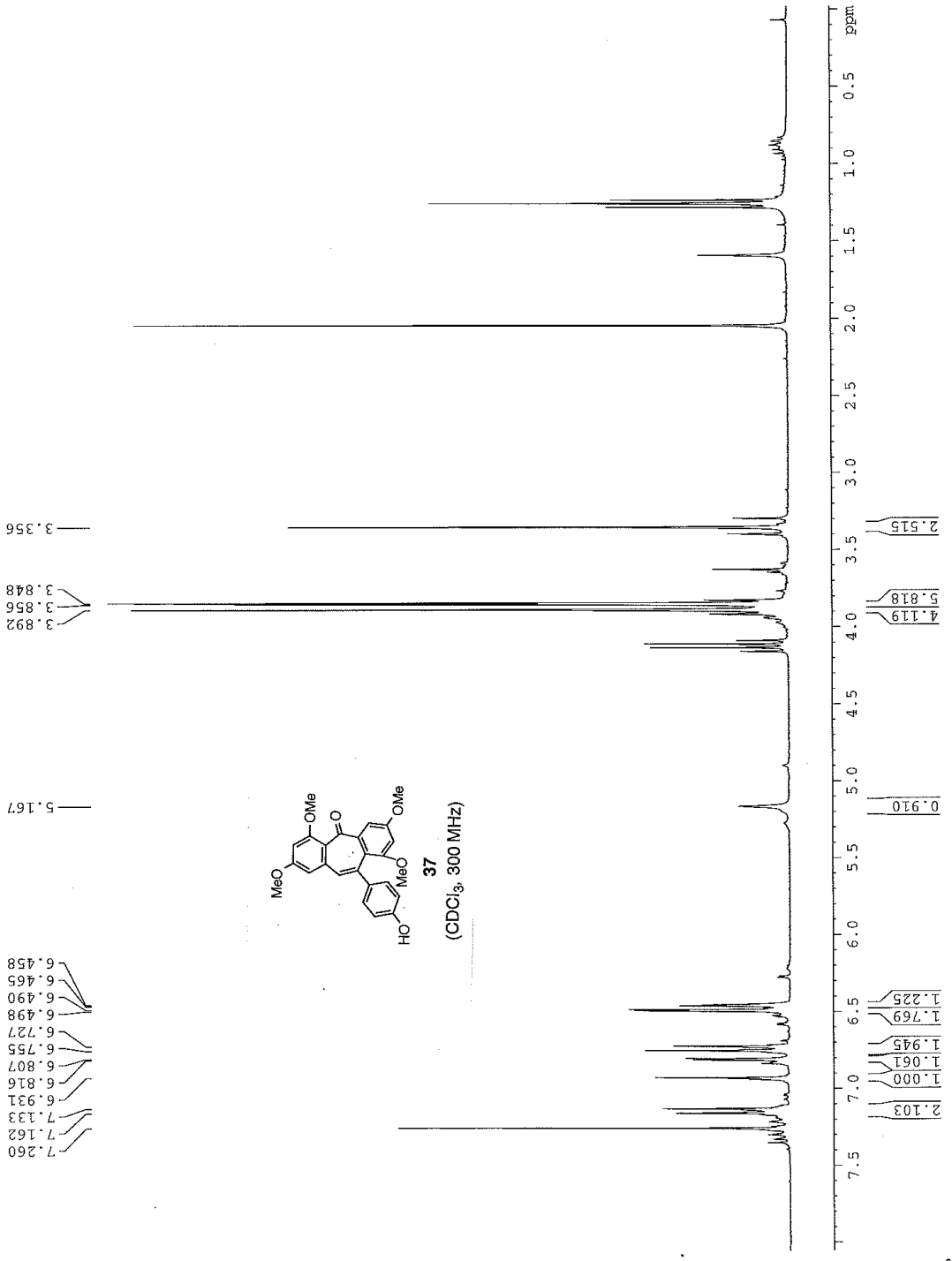
(a) S. Atun, N. Aznam, R. Arianingrum, Y. Takaya, N Masatake, *J. Phys. Sci.*, **2008**, *19*, 7-21
(b) S. Atun, S. A. Achmad, M Niwa, R. Arianingrum, N. Aznam, *Biochemical Systematics and Ecology*, **2006**, *34*, 642-644

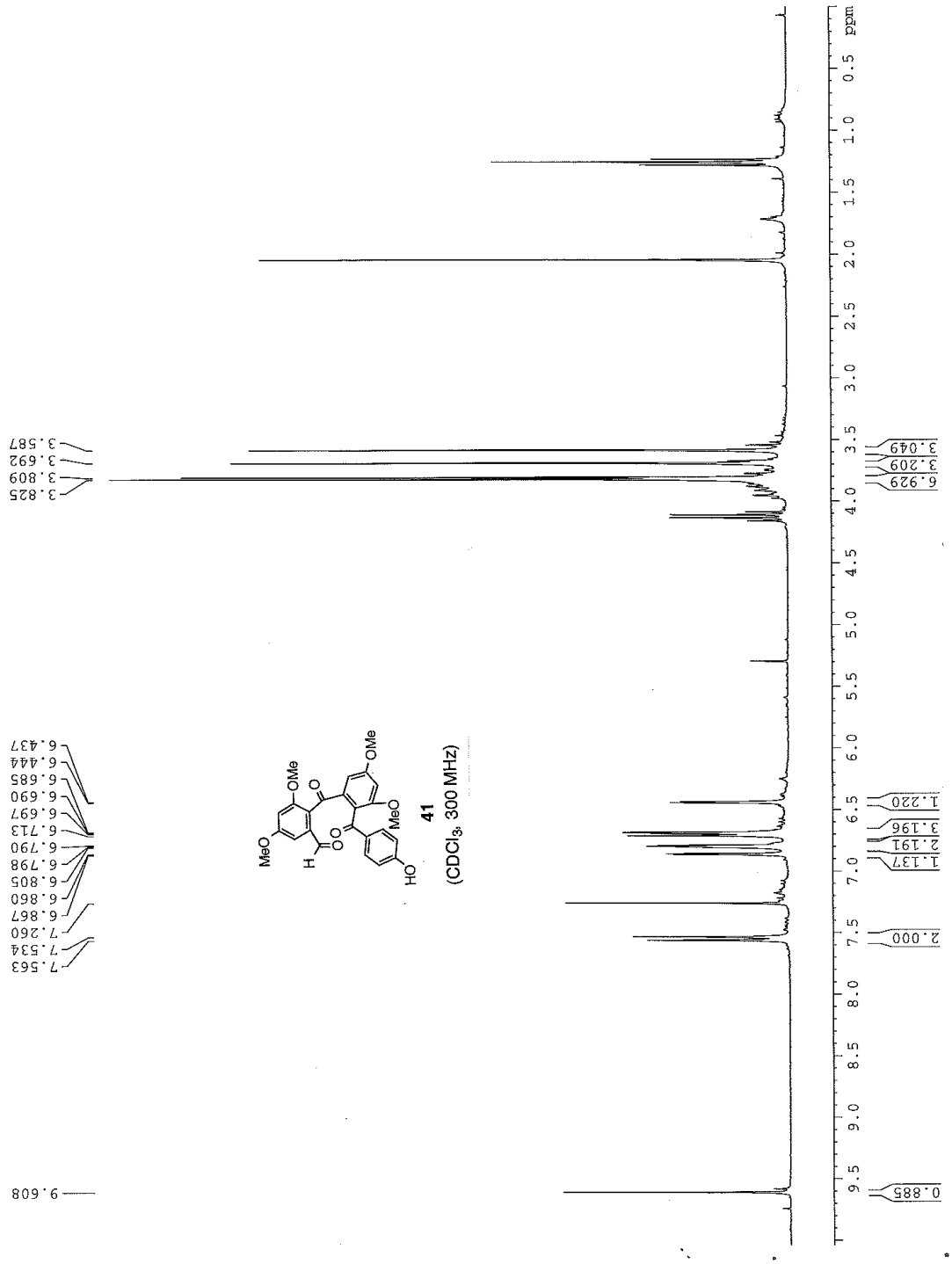

9.867
9.765
7.260
7.126
7.098
6.797
6.768
6.512
6.505
6.480
6.472
6.449
6.441
6.394
6.368
6.359
6.311
6.303
6.298
6.289
5.615
5.607
5.489
5.291
4.637
4.627
4.619
4.610
4.279
4.260
4.236
4.217
3.842
3.824
3.808
3.762
3.674
3.511
3.503
3.381
3.372
3.355
3.335
3.325
MeO
OMe
O
MeO
OMe
MeO
24
(CDCl3, 300 MHz)
0.413
1.000
0.862
0.882
5.324
0.893
0.433
1.077
1.486
1.052
1.053
0.507
1.063
0.453
6.099
4.012
1.284
3.128
6.318
2.362
0.423
0.436
1.041
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


MeO
OMe
OMe
MeO
MeO
27
(CDCl3, 300 MHz)
ppm


MeO
OMe
O
OMe
HO
MeO
MeO
30
(CDCl3, 300 MHz)
7.027
7.019
6.640
6.556
6.548
6.203
6.196
5.488
4.429
4.384
3.897
3.758
3.735
3.492
3.436
2.840
2.795
1.048
1.702
1.083
0.918
0.728
0.683
3.119
6.210
2.983
2.937
0.746
ppm

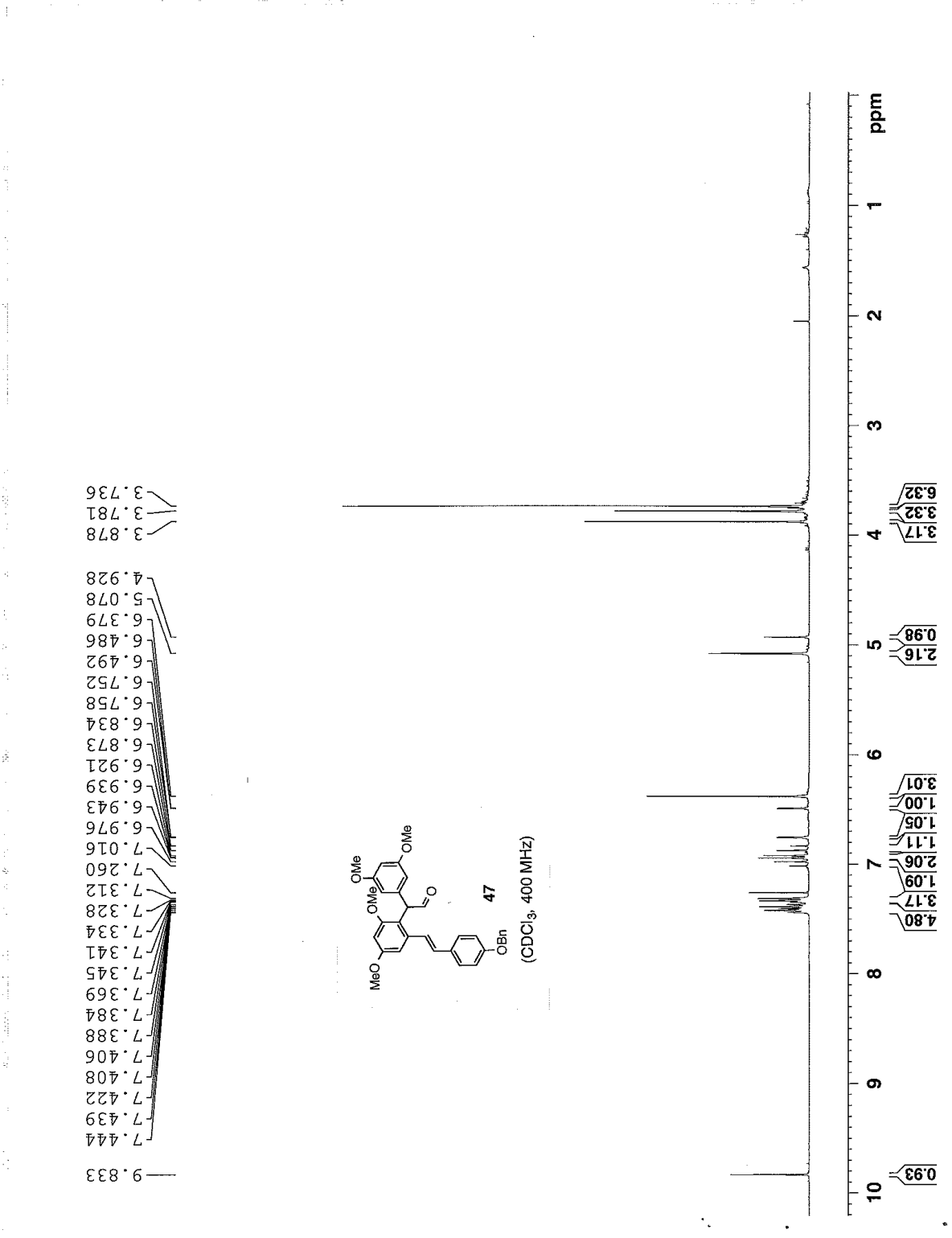

3.565
3.792
3.819
4.801
4.810
6.301
6.309
6.359
6.367
6.375
6.810
6.818
6.823
6.928
6.957
7.260
7.467
7.496
OMe
OMe
OMe
MeO
MeO
O
O
33
(CDCl3, 300 MHz)
2.141
2.423
2.923
1.313
1.000
1.938
3.643
10.450
4.511
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

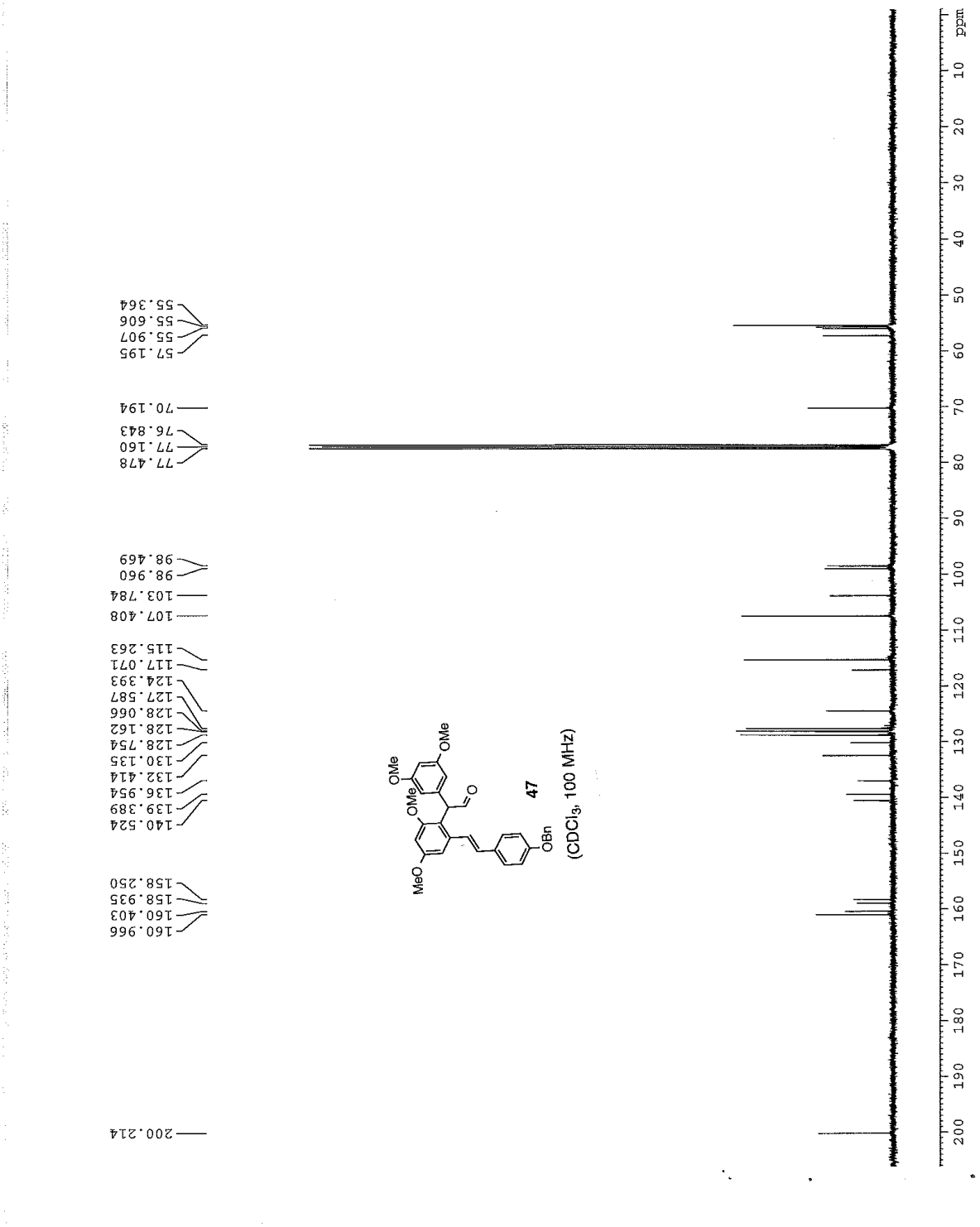

7.260
7.162
7.133
6.931
6.816
6.807
6.755
6.727
6.498
6.490
6.465
6.458
5.167
3.892
3.856
3.848
3.356
MeO
OMe
O
OMe
MeO
HO
37
(CDCl3, 300 MHz)
2.103
1.000
1.061
1.945
1.769
1.225
0.910
5.818
4.119
2.515
ppm

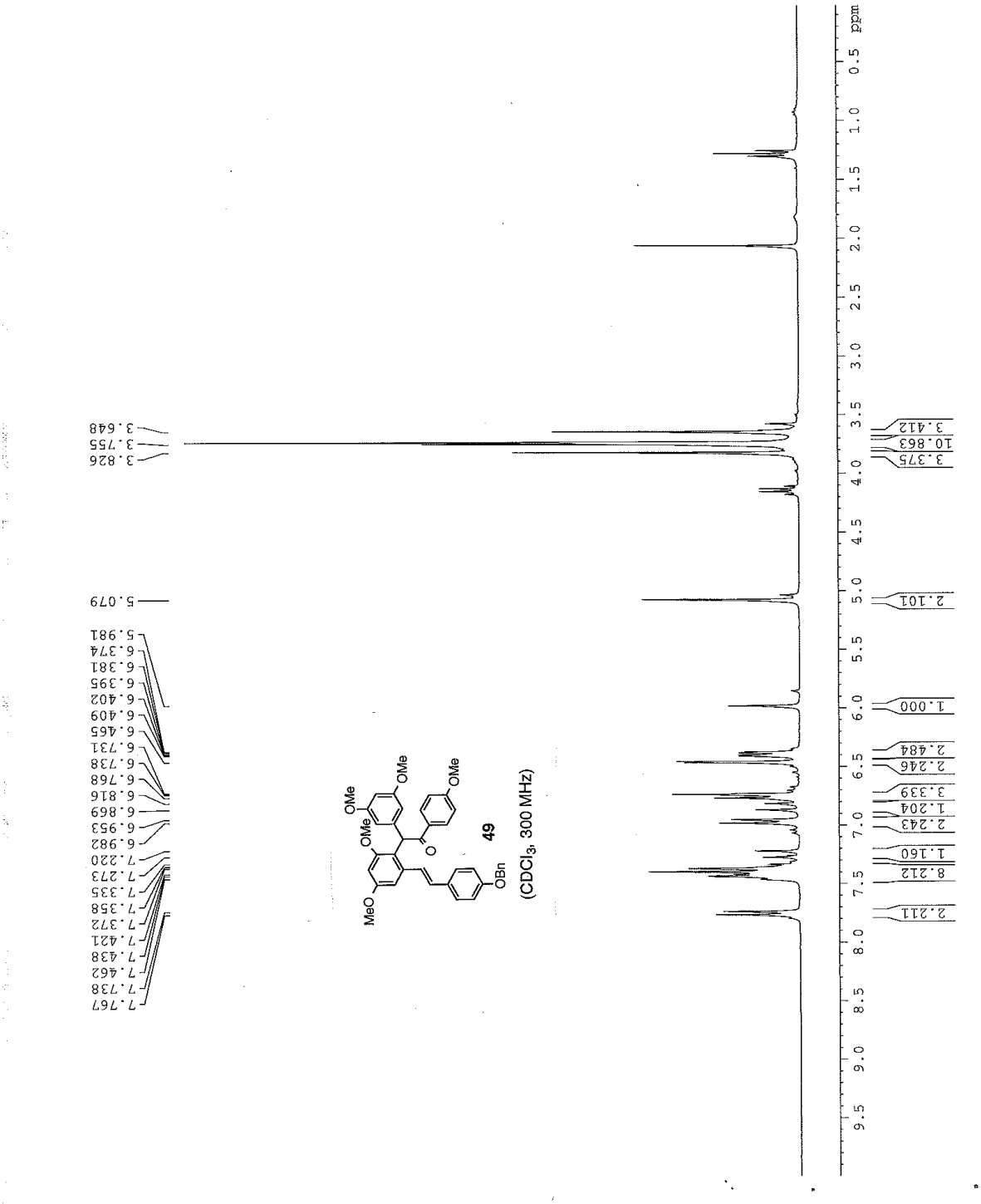


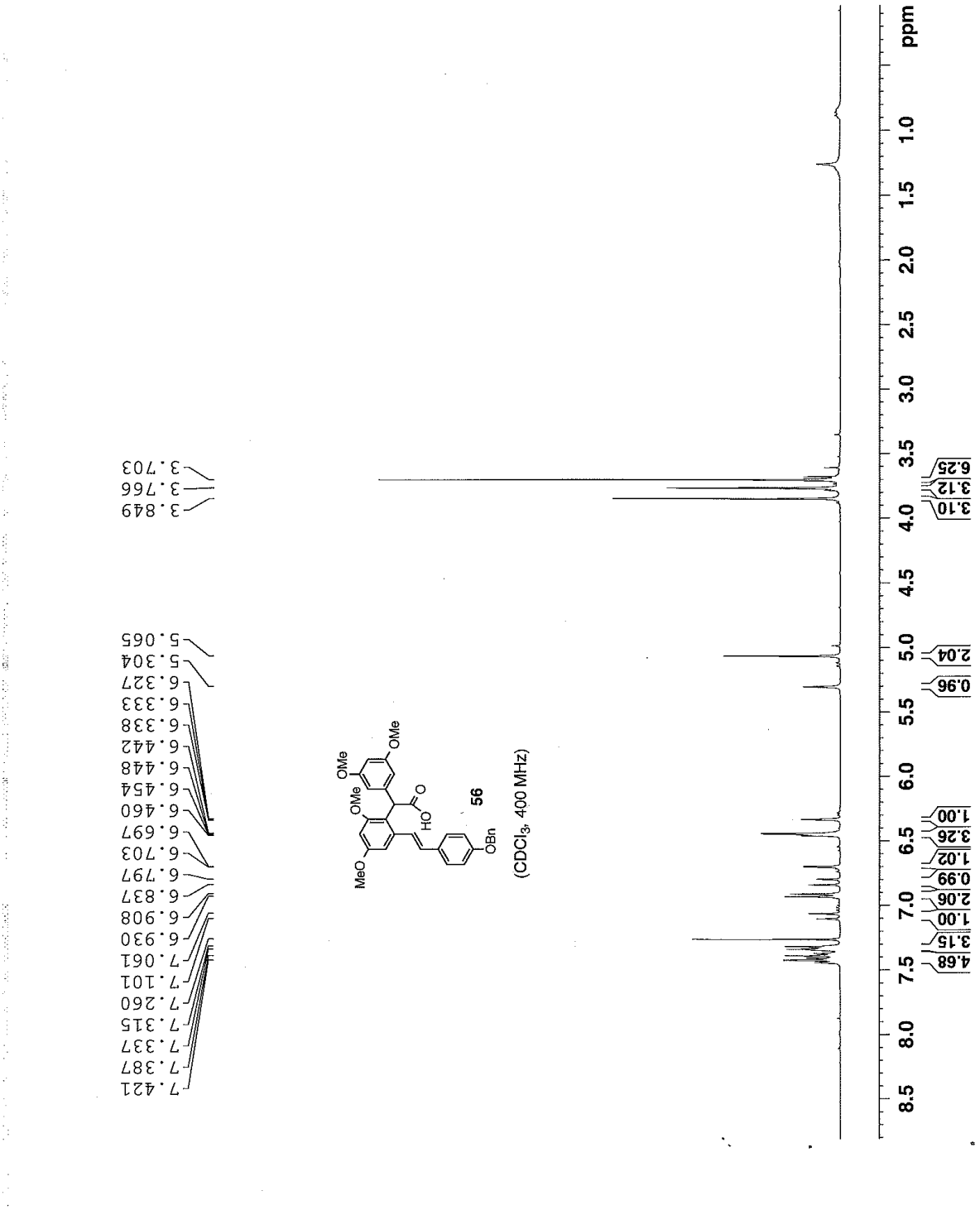
41

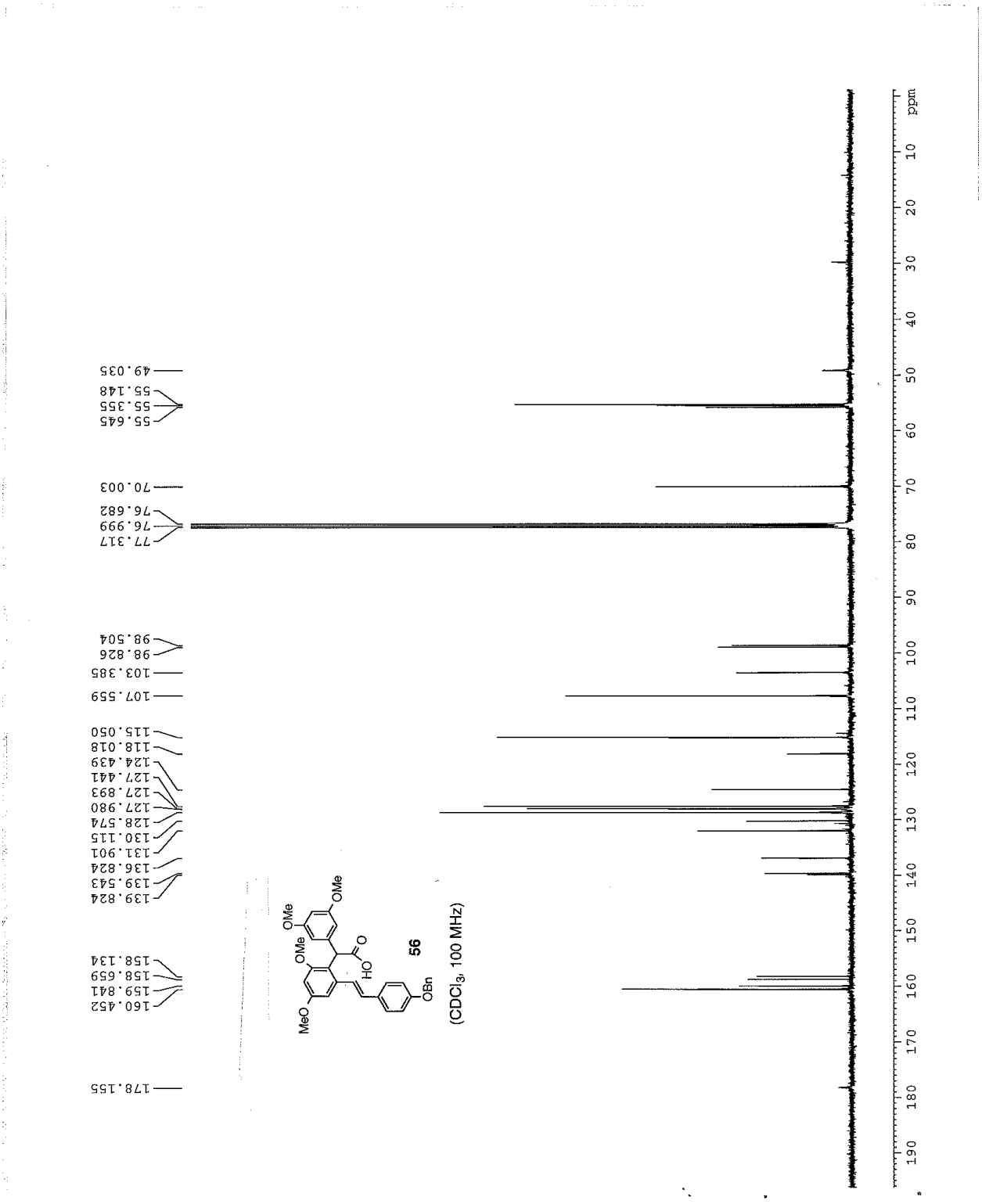
($CDCl_3$, 300 MHz)

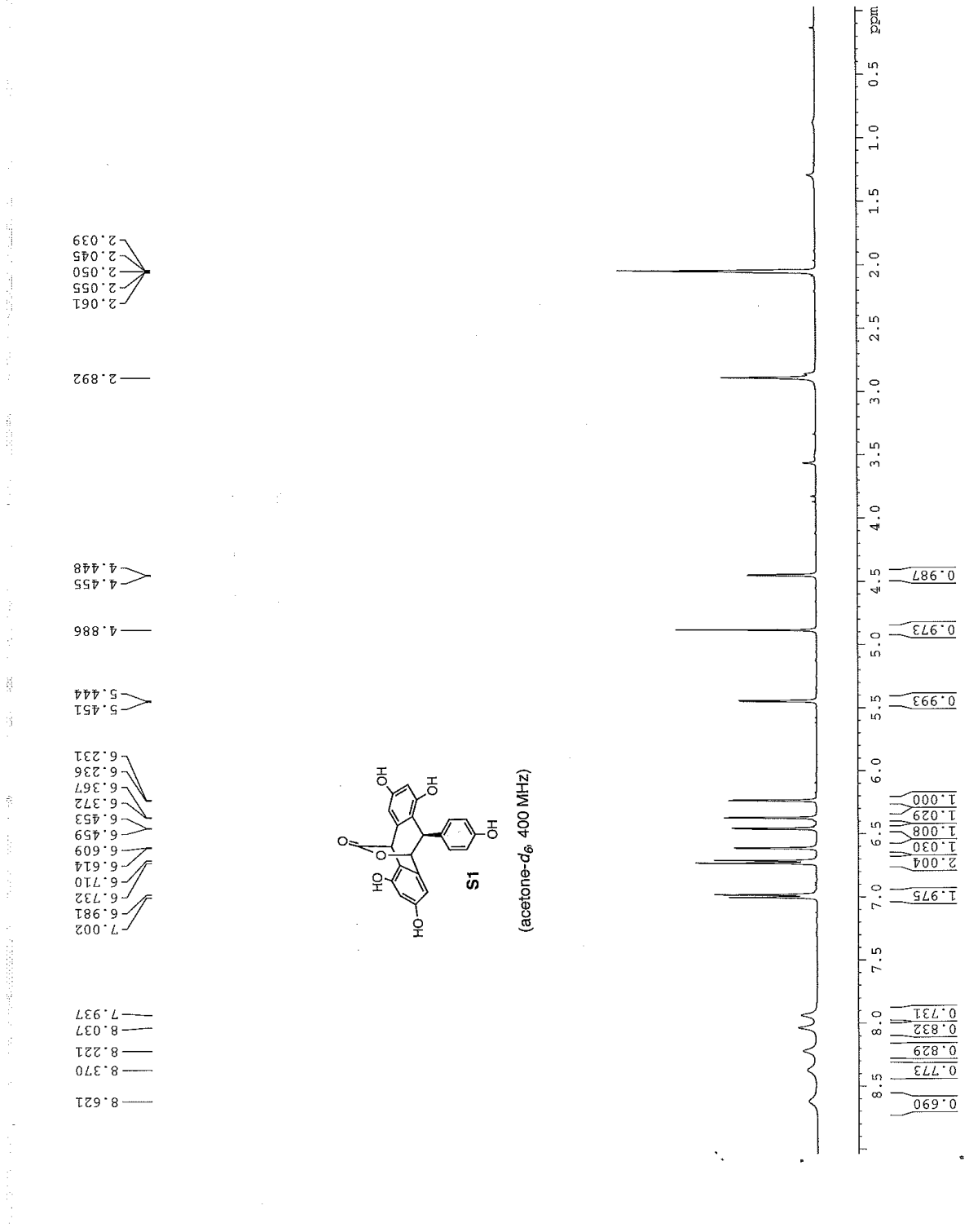

ppm
1
2
3
4
5
6
7
8
9
10
0.93
4.80
3.17
1.09
2.06
1.11
1.05
1.00
3.01
2.16
0.98
3.17
3.32
6.32
OMe
OMe
OMe
MeO
OBn
O
47
(CDCl3, 400 MHz)
9.833
7.444
7.439
7.422
7.408
7.406
7.388
7.384
7.369
7.345
7.341
7.334
7.328
7.312
7.260
7.016
6.976
6.943
6.939
6.921
6.873
6.834
6.758
6.752
6.492
6.486
6.379
5.078
4.928
3.878
3.781
3.736

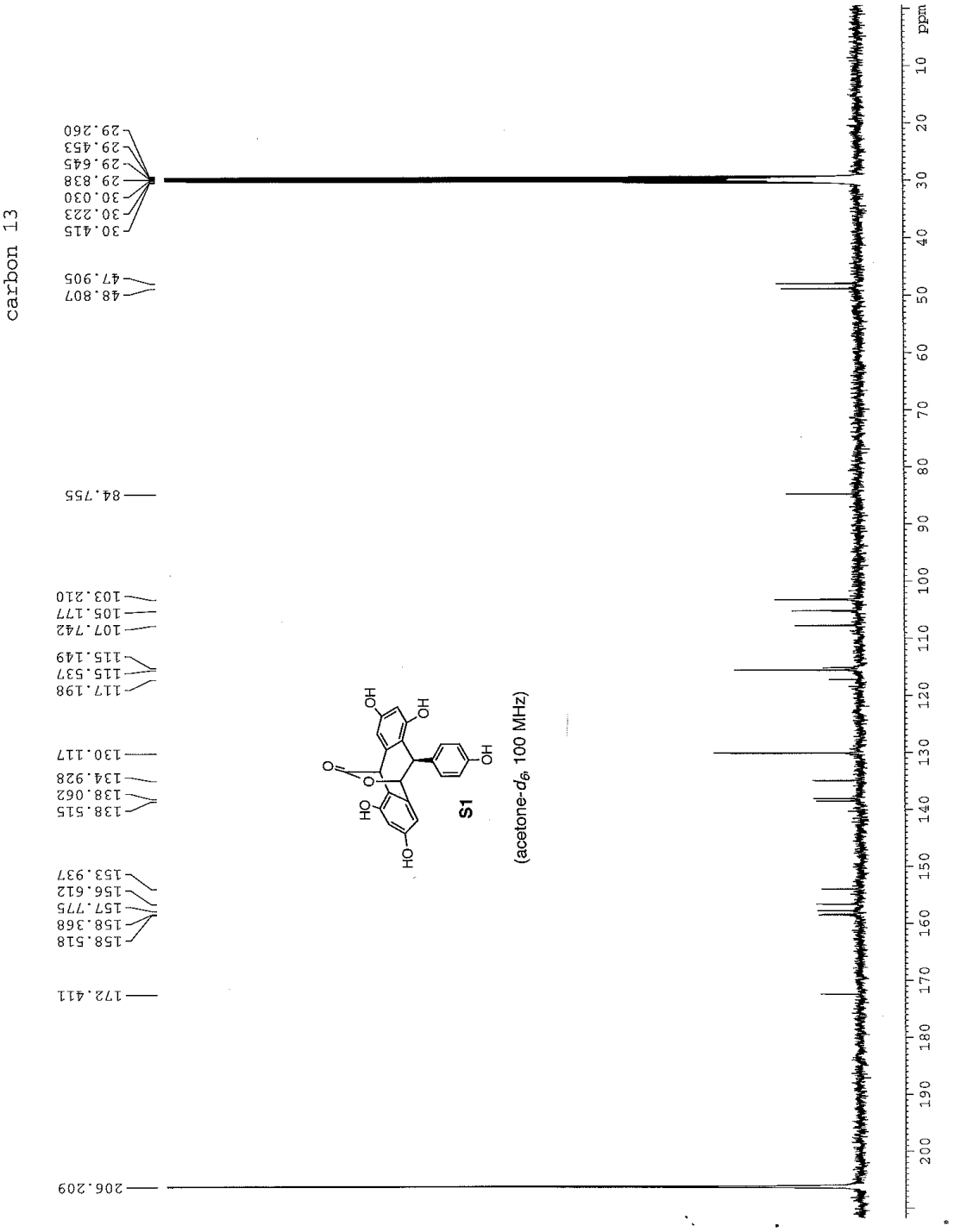

200.214
160.966
160.403
158.935
158.250
140.524
139.389
136.954
132.414
130.135
128.754
128.162
128.066
127.587
124.393
117.071
115.263
107.408
103.784
98.960
98.469
77.478
77.160
76.843
70.194
57.195
55.907
55.606
55.364
MeO
OMe
OMe
OMe
O
OBn
47
(CDCl3, 100 MHz)
ppm

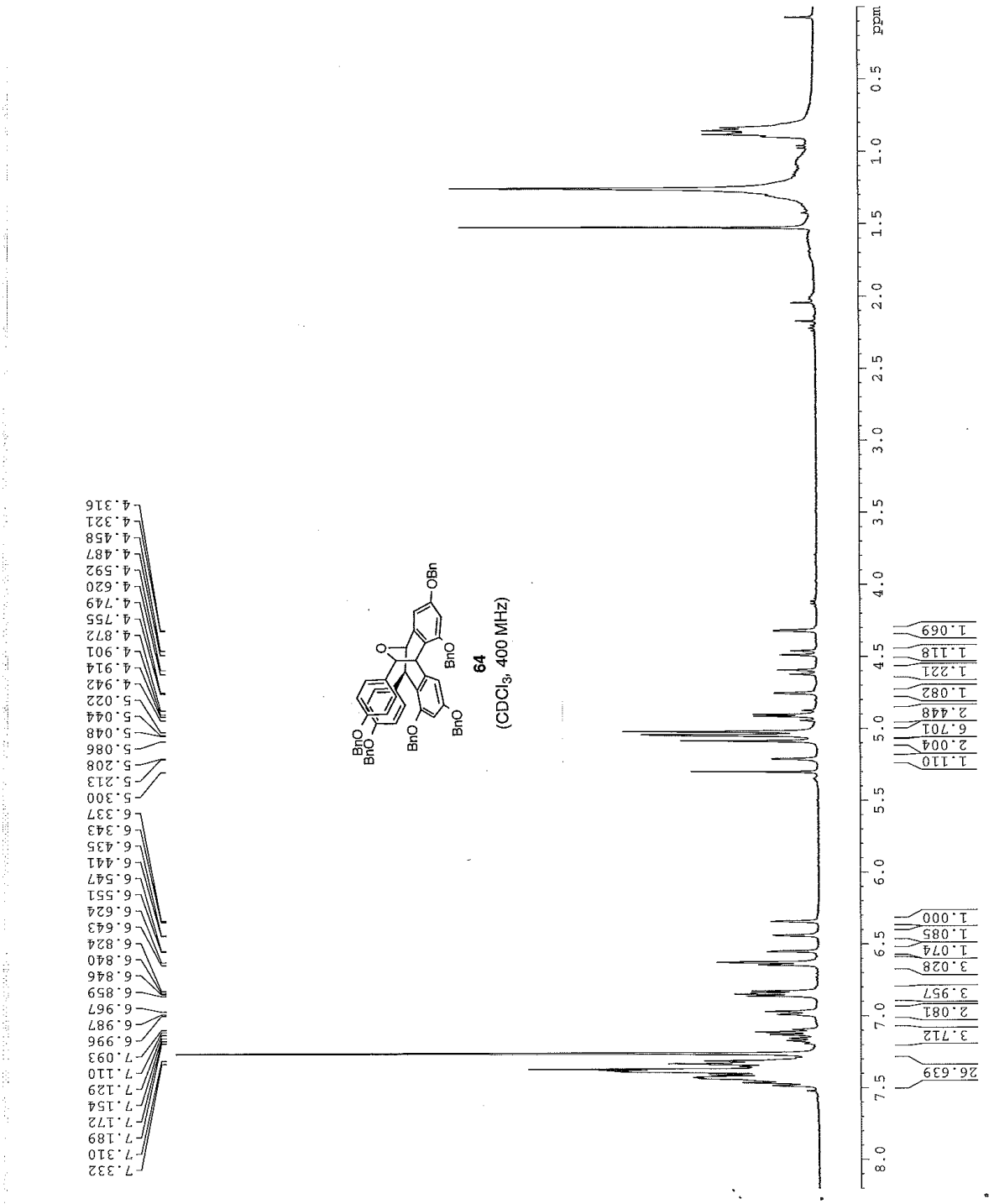

3.826
3.755
3.648
5.079
5.981
6.374
6.381
6.395
6.402
6.409
6.465
6.731
6.738
6.768
6.816
6.869
6.953
6.982
7.220
7.273
7.335
7.358
7.372
7.421
7.438
7.462
7.738
7.767
OMe
OMe
OMe
MeO
O
OBn
49
(CDCl3, 300 MHz)
2.211
8.212
1.160
2.243
1.204
3.339
2.246
2.484
1.000
2.101
3.375
10.863
3.412
ppm

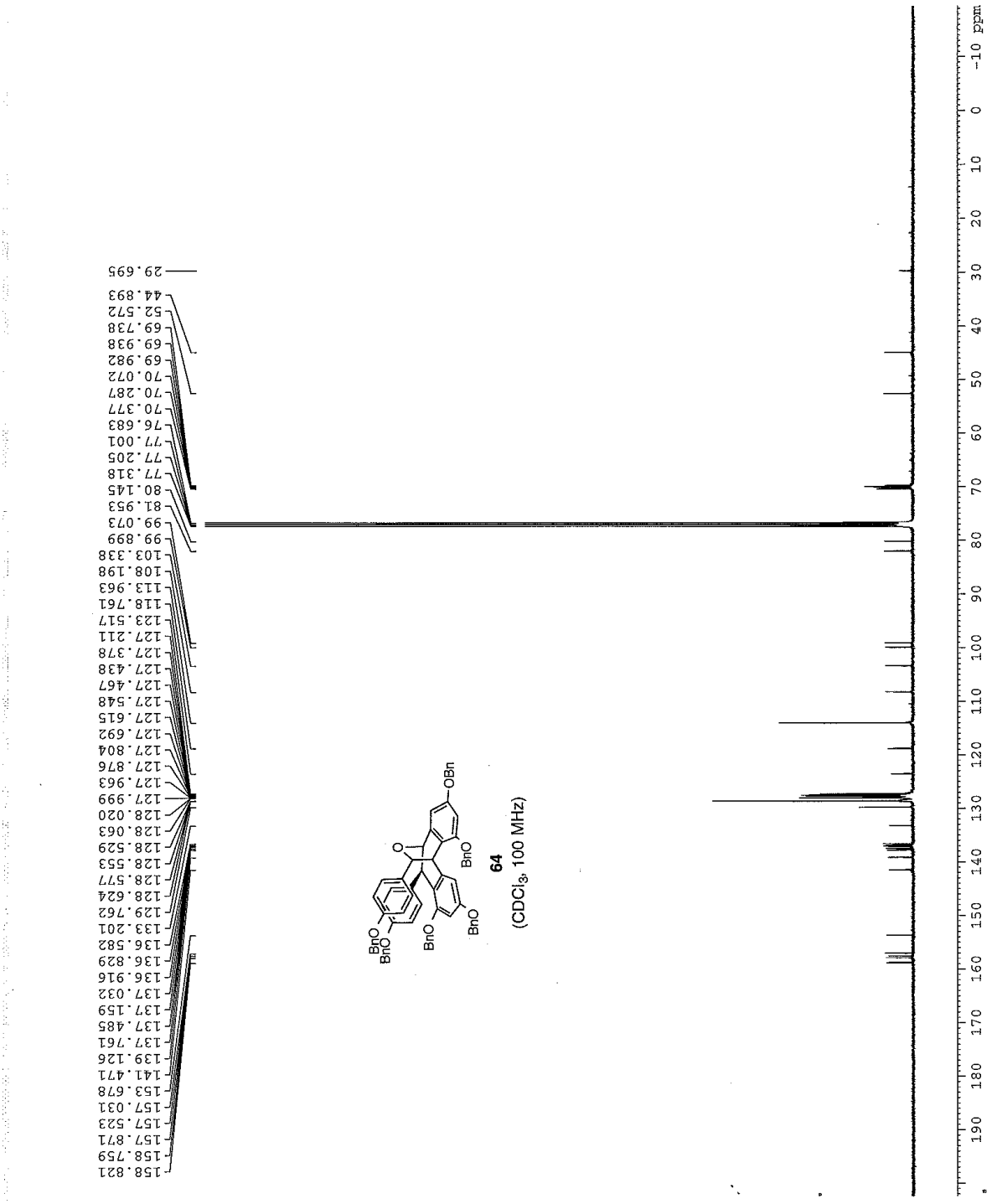

7.421
7.387
7.337
7.315
7.260
7.101
7.061
6.930
6.908
6.837
6.797
6.703
6.697
6.460
6.454
6.448
6.442
6.338
6.333
6.327
5.304
5.065
3.849
3.766
3.703
MeO
OMe
OMe
HO
O
OBn
56
(CDCl3, 400 MHz)
4.68
3.15
1.00
2.06
0.99
1.02
3.26
1.00
0.96
2.04
3.10
3.12
6.25
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

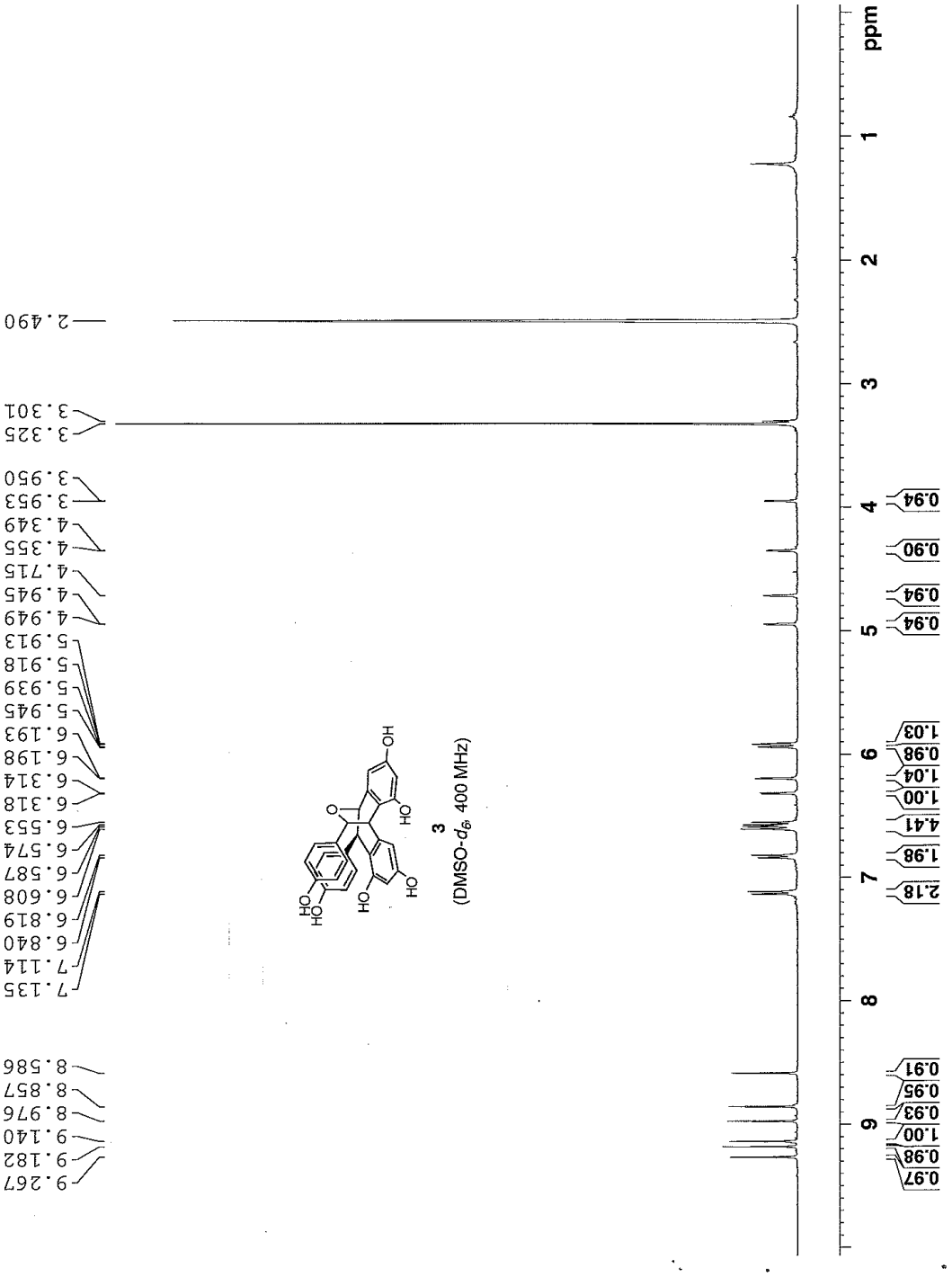

178.155
160.452
159.841
158.659
158.134
139.824
139.543
136.824
131.901
130.115
128.574
127.980
127.893
127.441
124.439
118.018
115.050
107.559
103.385
98.826
98.504
77.317
76.999
76.682
70.003
55.645
55.355
55.148
49.035
OMe
OMe
OMe
MeO
HO
O
OBn
56
(CDCl3, 100 MHz)
ppm

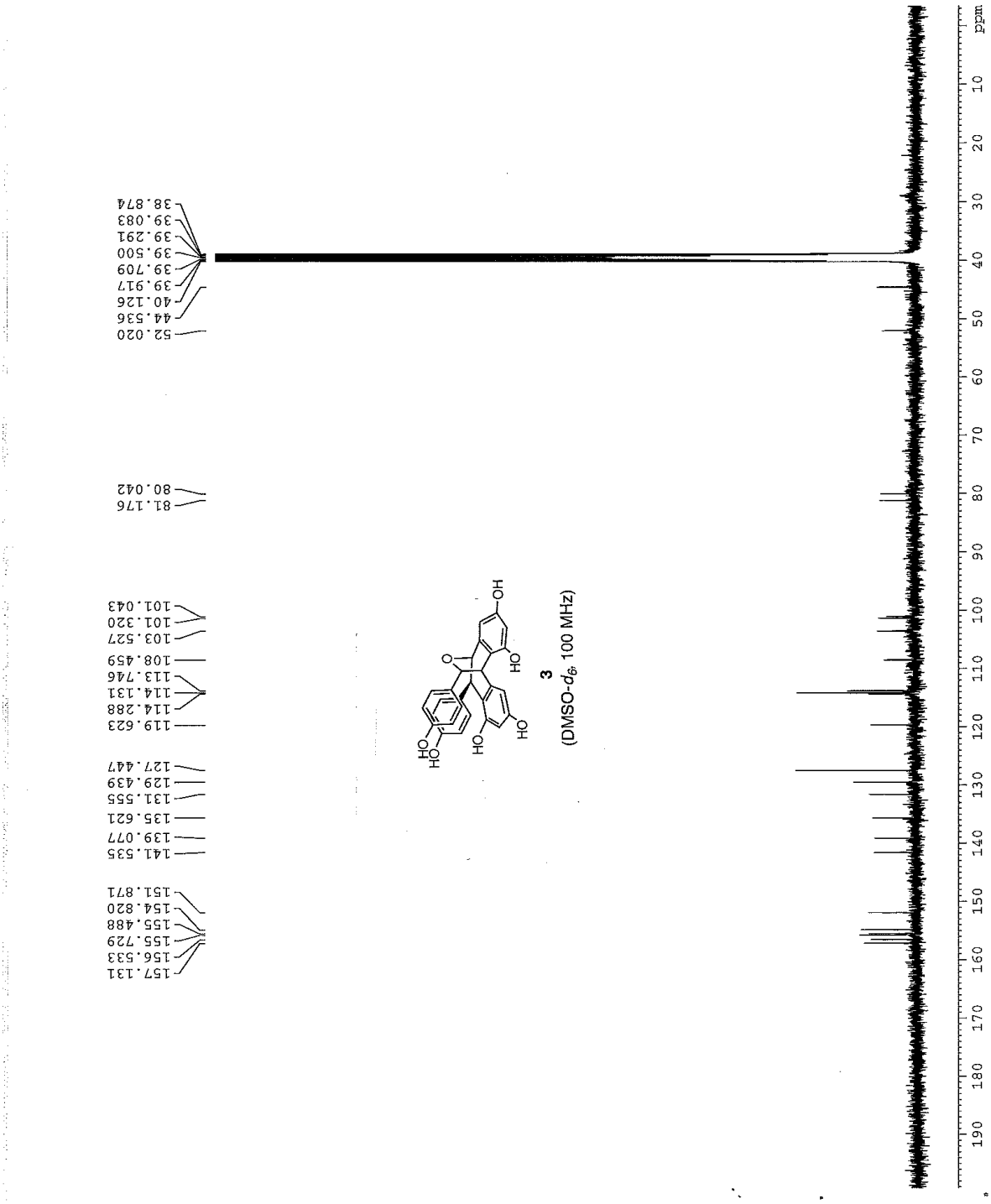

8.621
8.370
8.221
8.037
7.937
7.002
6.981
6.732
6.710
6.614
6.609
6.459
6.453
6.372
6.367
6.236
6.231
5.451
5.444
4.886
4.455
4.448
2.892
2.061
2.055
2.050
2.045
2.039
S1
(acetone-d_6, 400 MHz)
0.690
0.773
0.829
0.832
0.731
1.975
2.004
1.030
1.008
1.029
1.000
0.993
0.973
0.987
ppm

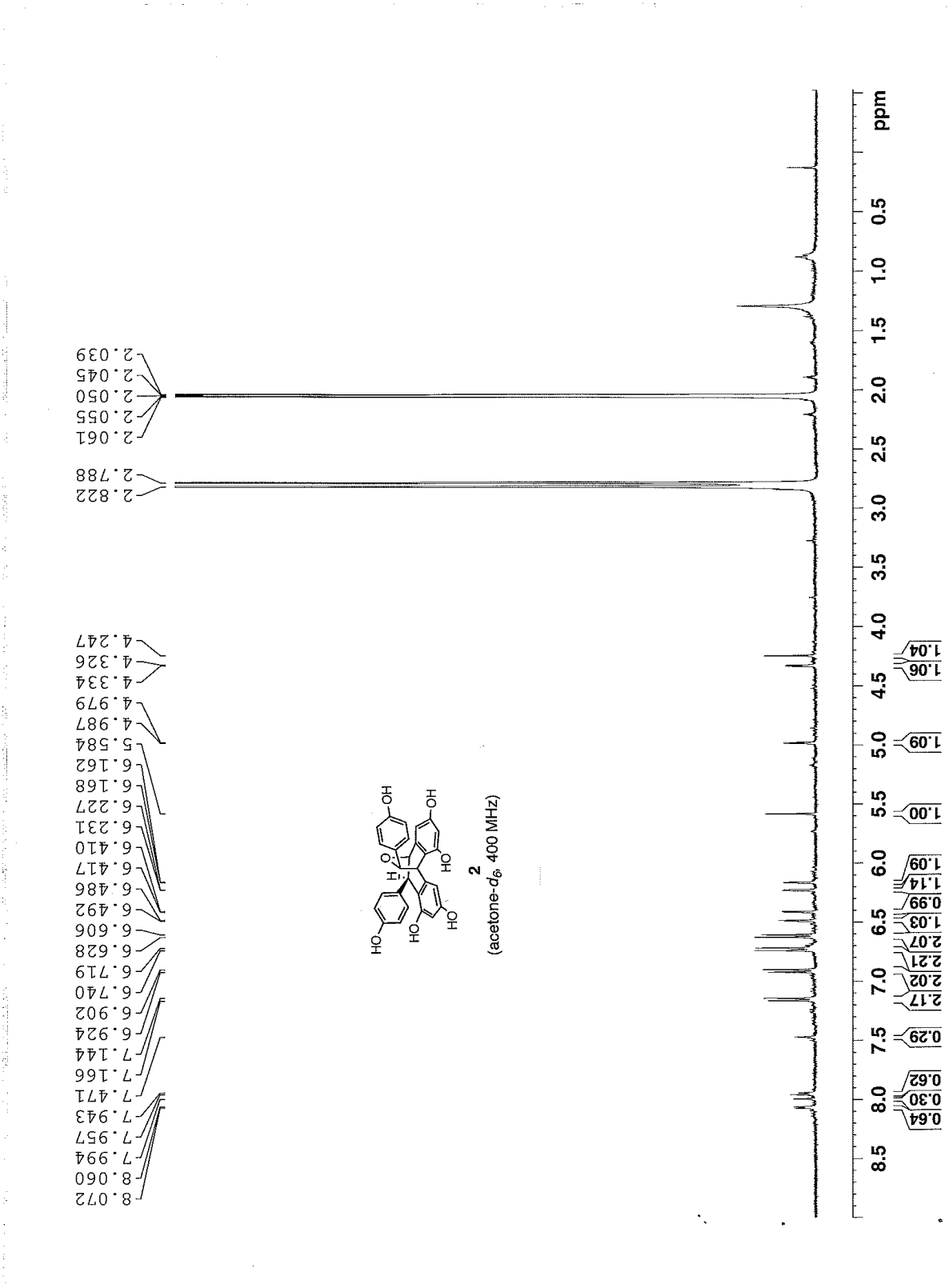

carbon 13
206.209
172.411
158.518
158.368
157.775
156.612
153.937
138.515
138.062
134.928
130.117
117.198
115.537
115.149
107.742
105.177
103.210
84.755
48.807
47.905
30.415
30.223
30.030
29.838
29.645
29.453
29.260
S1
(acetone-d_6, 100 MHz)
ppm

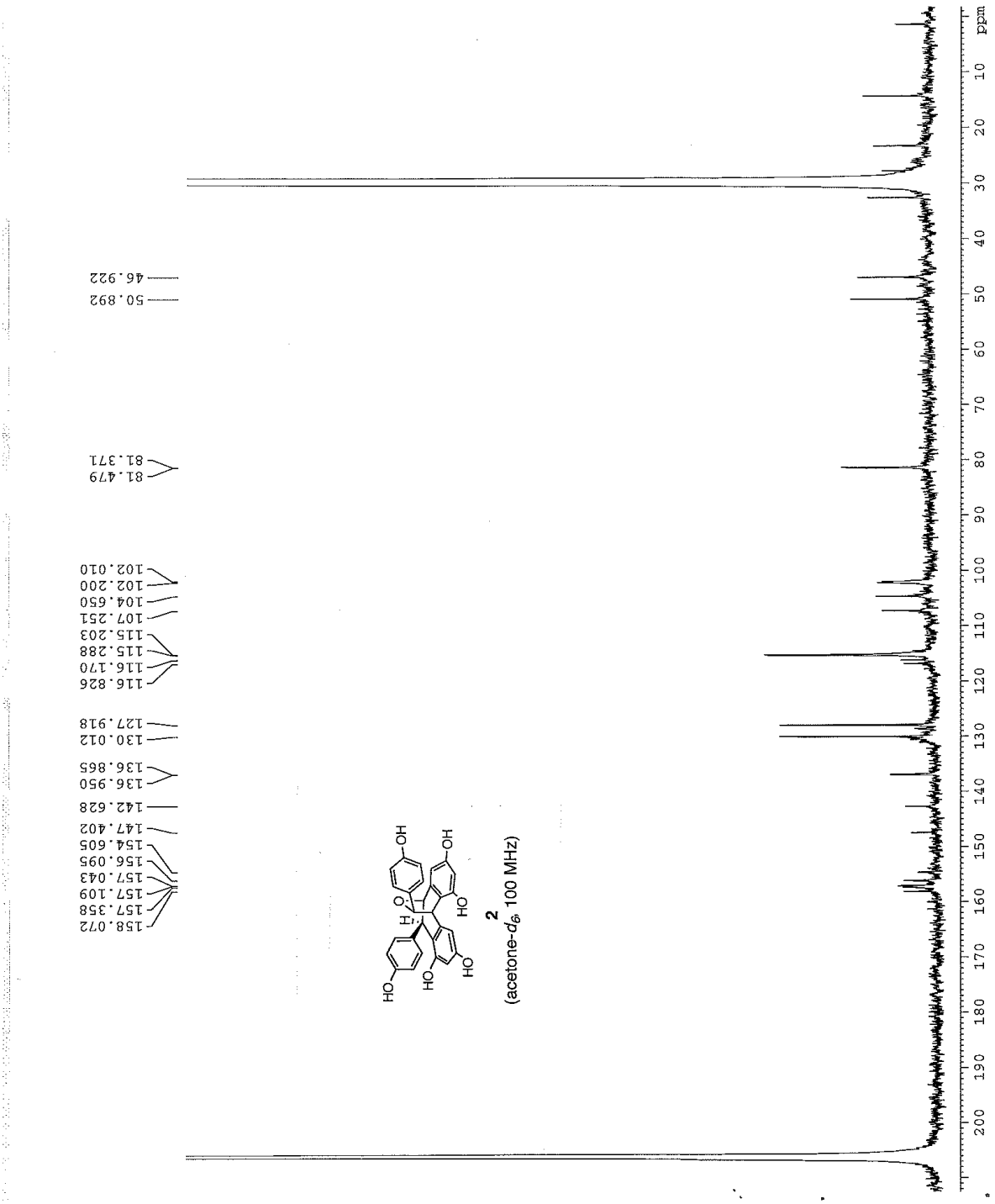

64
(CDCl3, 400 MHz)
OBn
BnO
BnO
BnO
BnO
7.332
7.310
7.189
7.172
7.154
7.129
7.110
7.093
6.996
6.987
6.967
6.859
6.846
6.840
6.824
6.643
6.624
6.551
6.547
6.441
6.435
6.343
6.337
5.300
5.213
5.208
5.086
5.048
5.044
5.022
4.942
4.914
4.901
4.872
4.755
4.749
4.620
4.592
4.487
4.458
4.321
4.316
26.639
3.712
2.081
3.957
3.028
1.074
1.085
1.000
1.110
2.004
6.701
2.448
1.082
1.221
1.118
1.069
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

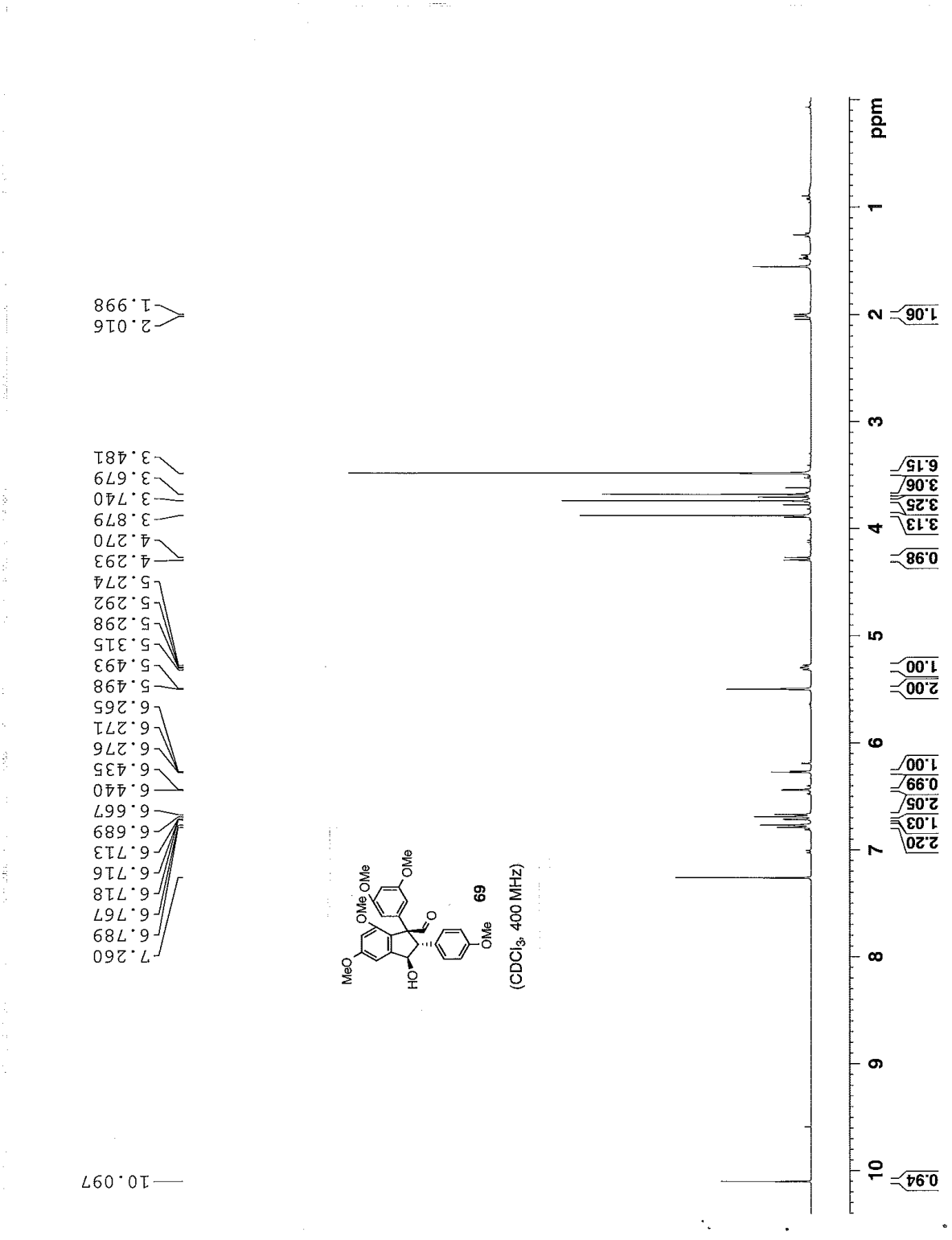

64
(CDCl3, 100 MHz)
OBn
BnO
BnO
BnO
BnO
BnO
29.695
44.893
52.572
69.738
69.938
69.982
70.072
70.287
70.377
76.683
77.001
77.205
77.318
80.145
81.953
99.073
99.899
103.338
108.198
113.963
118.761
123.517
127.211
127.378
127.438
127.467
127.548
127.615
127.692
127.804
127.876
127.963
127.999
128.020
128.063
128.529
128.553
128.577
128.624
129.762
133.201
136.582
136.829
136.916
137.032
137.159
137.485
137.761
139.126
141.471
153.678
157.031
157.523
157.871
158.759
158.821
ppm

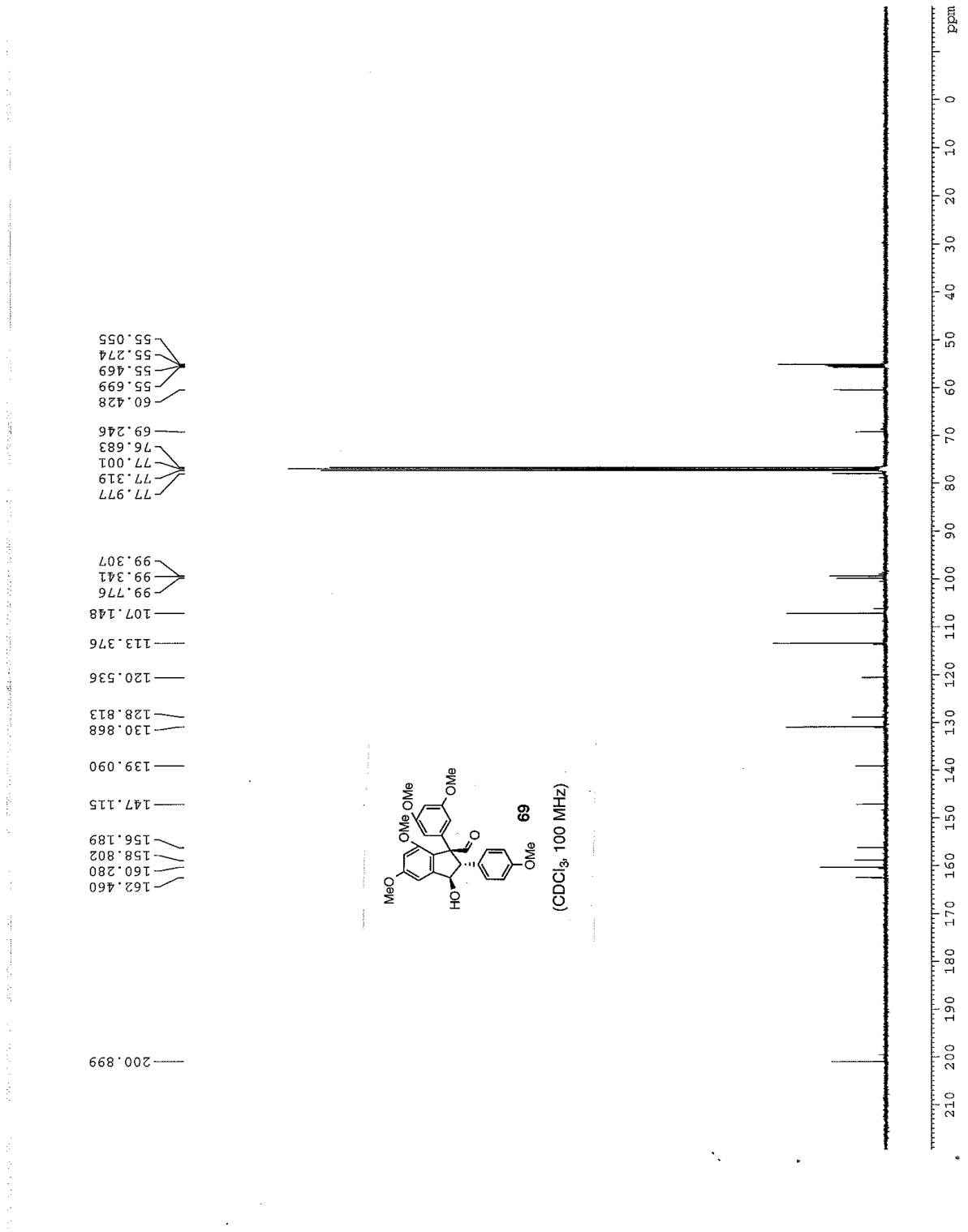

3
(DMSO-d_6, 400 MHz)
ppm
0.97
0.98
1.00
0.93
0.95
0.91
2.18
1.98
4.41
1.00
1.04
0.98
1.03
0.94
0.90
0.94
0.94
2.490
3.301
3.325
3.950
3.953
4.349
4.355
4.715
4.945
4.949
5.913
5.918
5.939
5.945
6.193
6.198
6.314
6.318
6.553
6.574
6.587
6.608
6.819
6.840
7.114
7.135
8.586
8.857
8.976
9.140
9.182
9.267

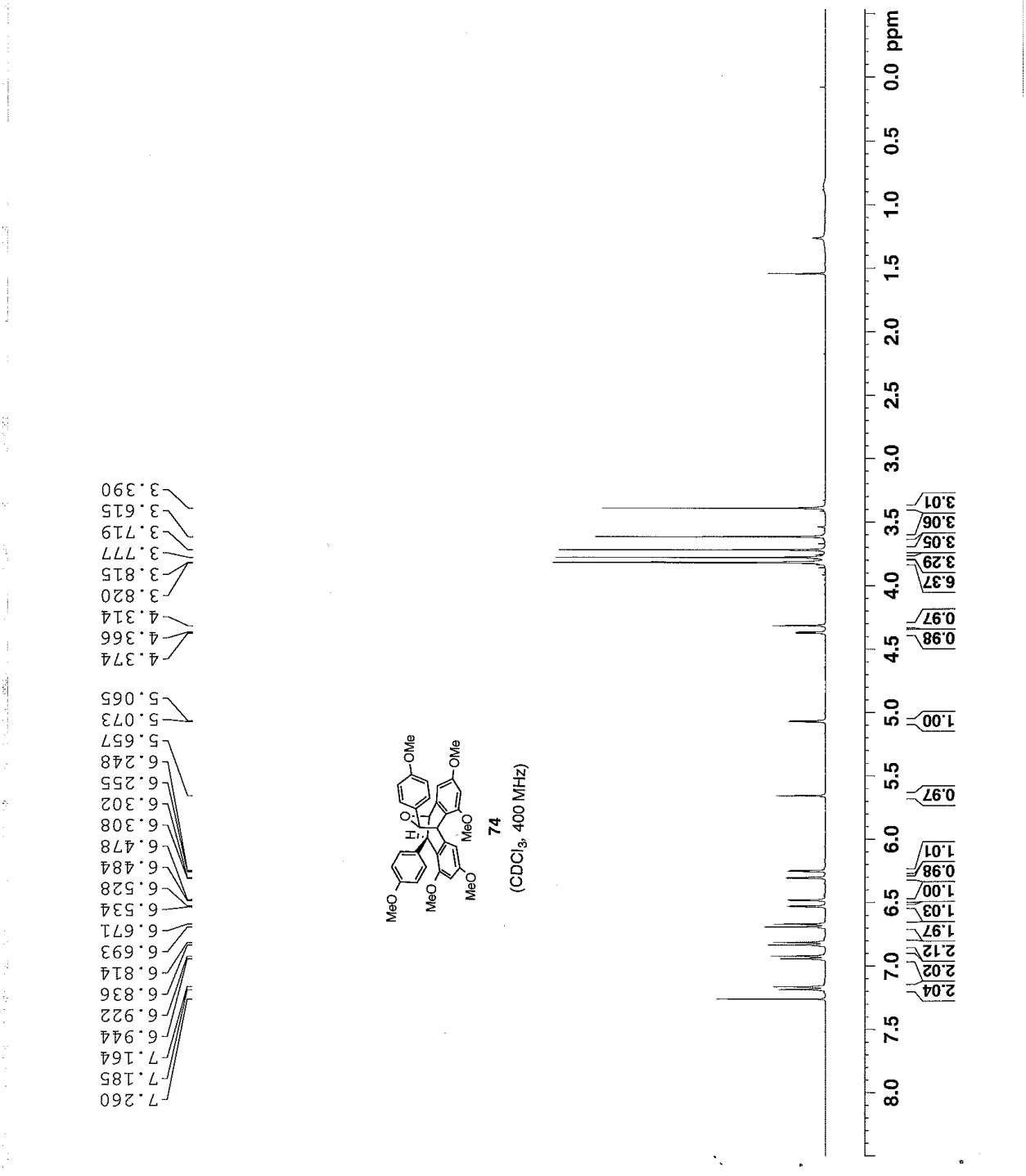

38.874
39.083
39.291
39.500
39.709
39.917
40.126
44.536
52.020
80.042
81.176
101.043
101.320
103.527
108.459
113.746
114.131
114.288
119.623
127.447
129.439
131.555
135.621
139.077
141.535
151.871
154.820
155.488
155.729
156.533
157.131
OH
HO
HO
HO
HO
O
3
(DMSO-d_6, 100 MHz)
ppm

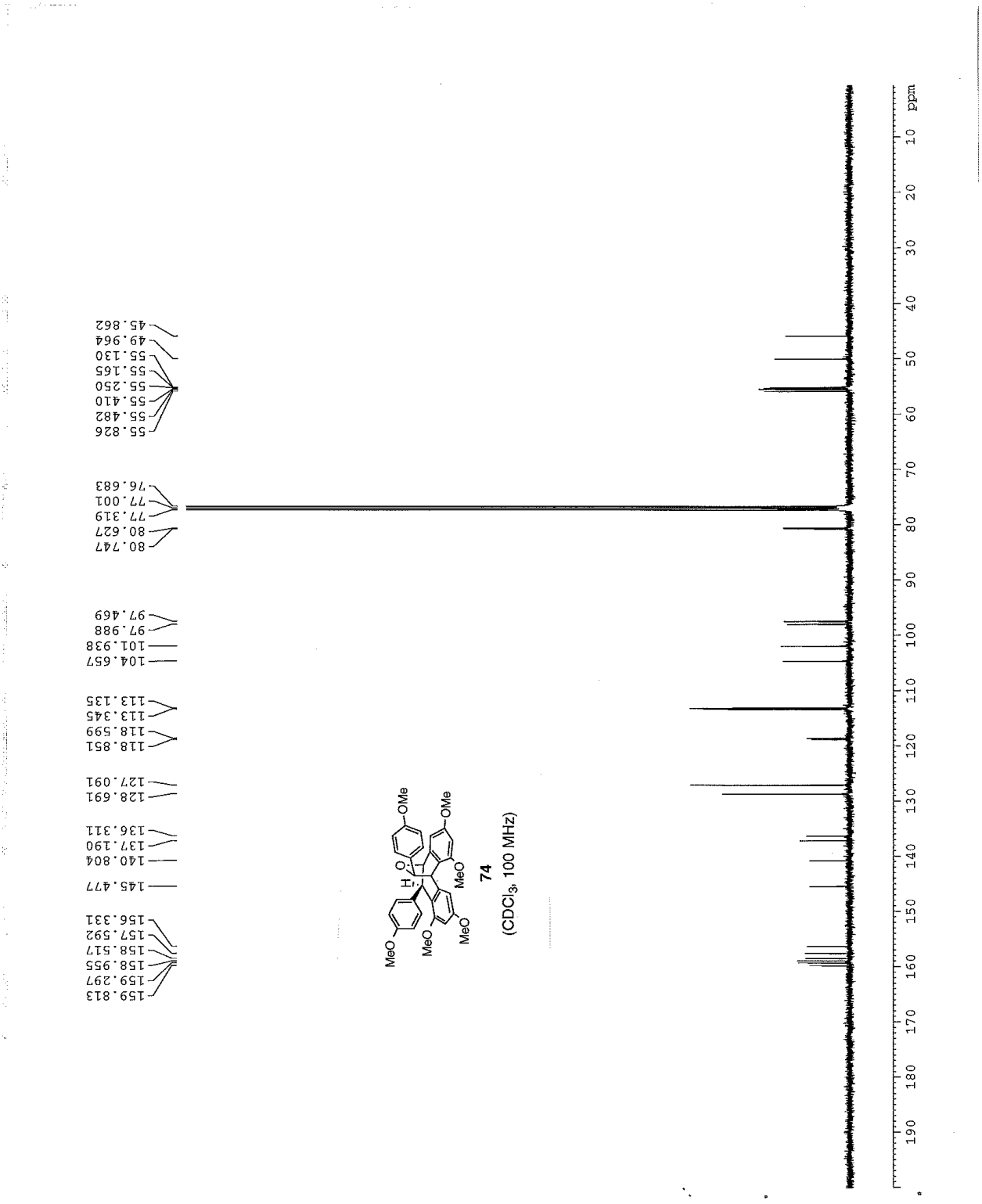

2
(acetone-d_6, 400 MHz)
ppm


158.072
157.358
157.109
157.043
156.095
154.605
147.402
142.628
136.950
136.865
130.012
127.918
116.826
116.170
115.288
115.203
107.251
104.650
102.200
102.010
81.479
81.371
50.892
46.922
OH
HO
O
H
2
(acetone-d_6, 100 MHz)
ppm


10.097
7.260
6.789
6.767
6.718
6.716
6.713
6.689
6.667
6.440
6.435
6.276
6.271
6.265
5.498
5.493
5.315
5.298
5.292
5.274
4.293
4.270
3.879
3.740
3.679
3.481
2.016
1.998
MeO
OMe
OMe
HO
O
OMe
69
(CDCl3, 400 MHz)
ppm
0.94
2.20
1.03
2.05
0.99
1.00
1.00
2.00
1.00
0.98
3.13
3.25
3.06
6.15
1.06


55.055
55.274
55.469
55.699
60.428
69.246
76.683
77.001
77.319
77.977
99.307
99.341
99.776
107.148
113.376
120.536
128.813
130.868
139.090
147.115
156.189
158.802
160.280
162.460
200.899
MeO
OMe
OMe
OMe
HO
O
69
(CDCl3, 100 MHz)
ppm


7.260
7.185
7.164
6.944
6.922
6.836
6.814
6.693
6.671
6.534
6.528
6.484
6.478
6.308
6.302
6.255
6.248
5.657
5.073
5.065
4.374
4.366
4.314
3.820
3.815
3.777
3.719
3.615
3.390
OMe
OMe
MeO
MeO
MeO
MeO
H
O
74
(CDCl3, 400 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm
2.04
2.02
2.12
1.97
1.03
1.00
0.98
1.01
0.97
1.00
0.98
0.97
6.37
3.29
3.05
3.06
3.01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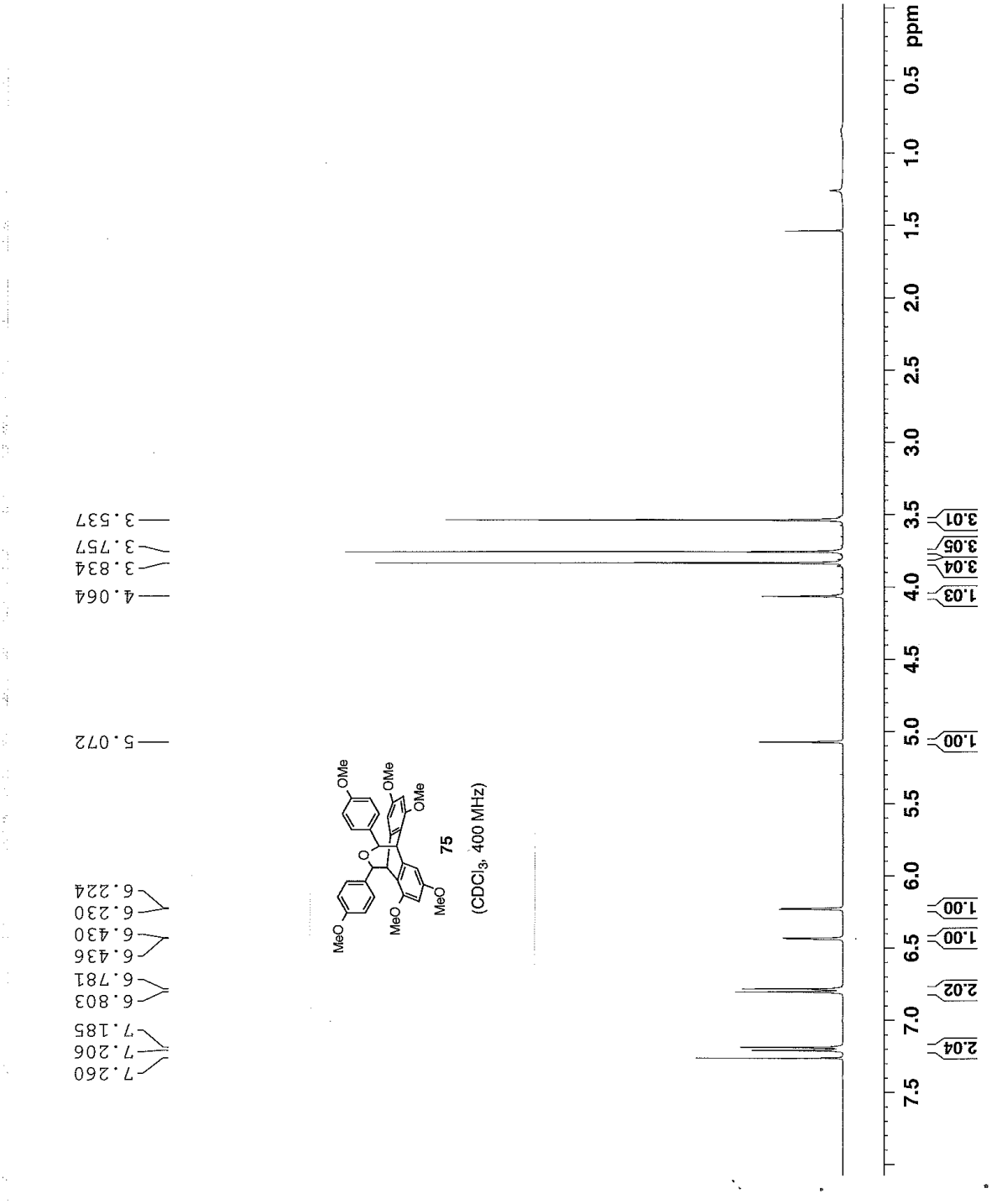
158.517
157.592
156.331
145.477
140.804
137.190
136.311
128.691
127.091
118.851
118.599
113.345
113.135
104.657
101.938
97.988
97.469
80.747
80.627
77.319
77.001
76.683
55.826
55.482
55.410
55.250
55.165
55.130
49.964
45.862
OMe
OMe
MeO
MeO
MeO
MeO
O
H
74
(CDCl3, 100 MHz)
ppm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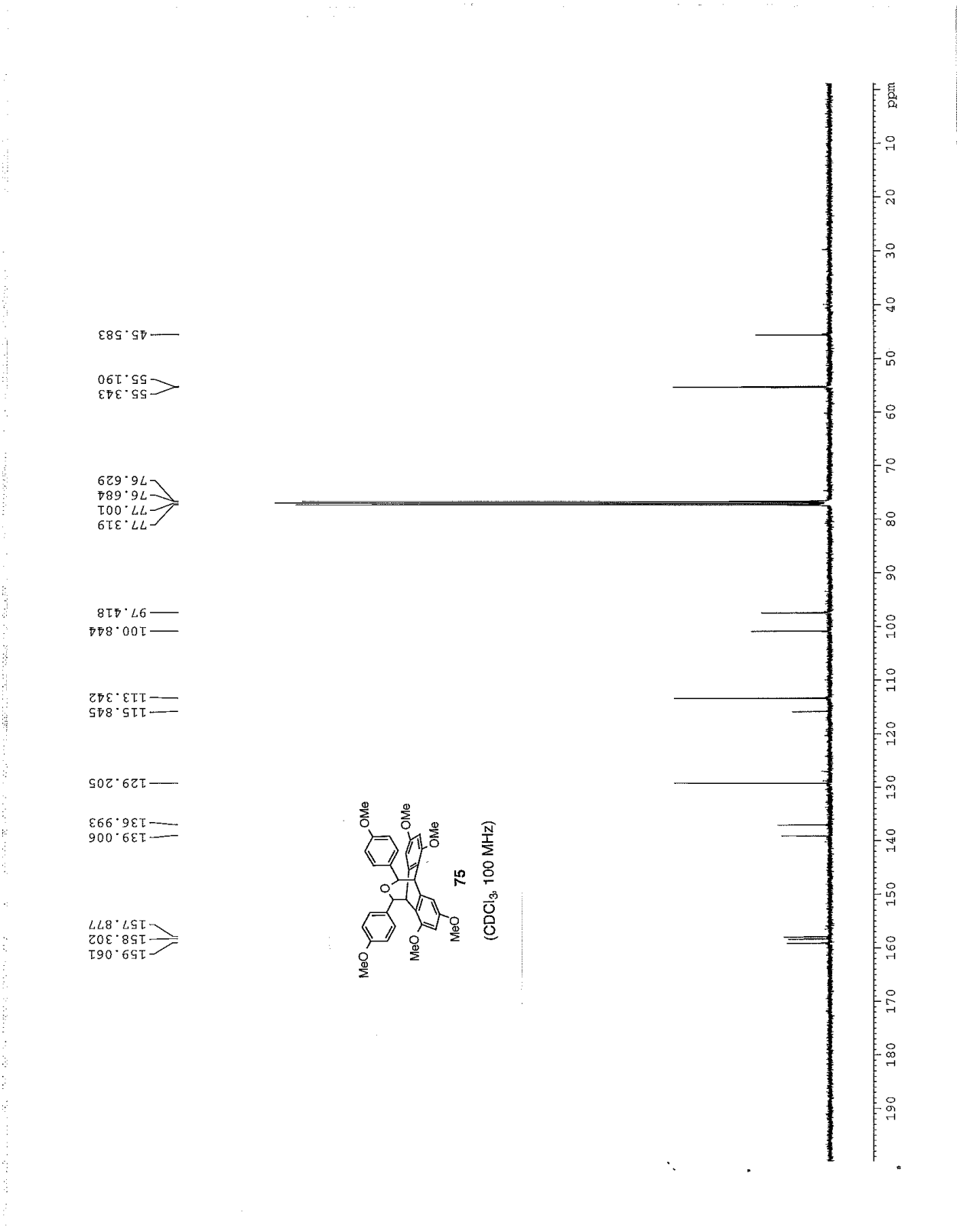
7.206
7.185
6.803
6.781
6.436
6.430
6.230
6.224
5.072
4.064
3.834
3.757
3.537
OMe
OMe
OMe
MeO
MeO
MeO
75
(CDCl3, 400 MHz)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.04
2.02
1.00
1.00
1.00
1.03
3.04
3.05
3.01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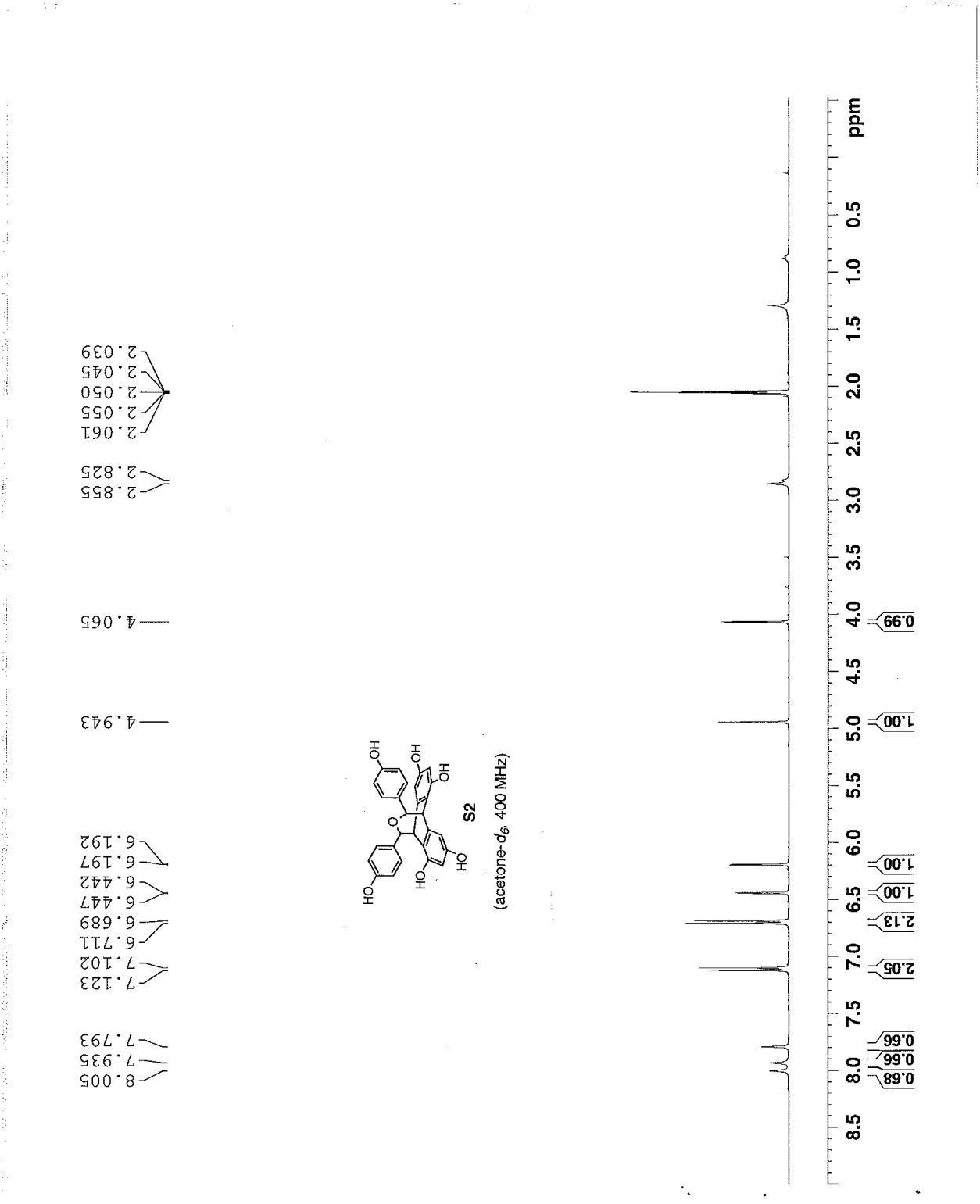
55.343
55.190
76.629
76.684
77.001
77.319
97.418
100.844
113.342
115.845
129.205
136.993
139.006
157.877
158.302
159.061
OMe
OMe
OMe
MeO
MeO
MeO
O
75
(CDCl3, 100 MHz)
ppm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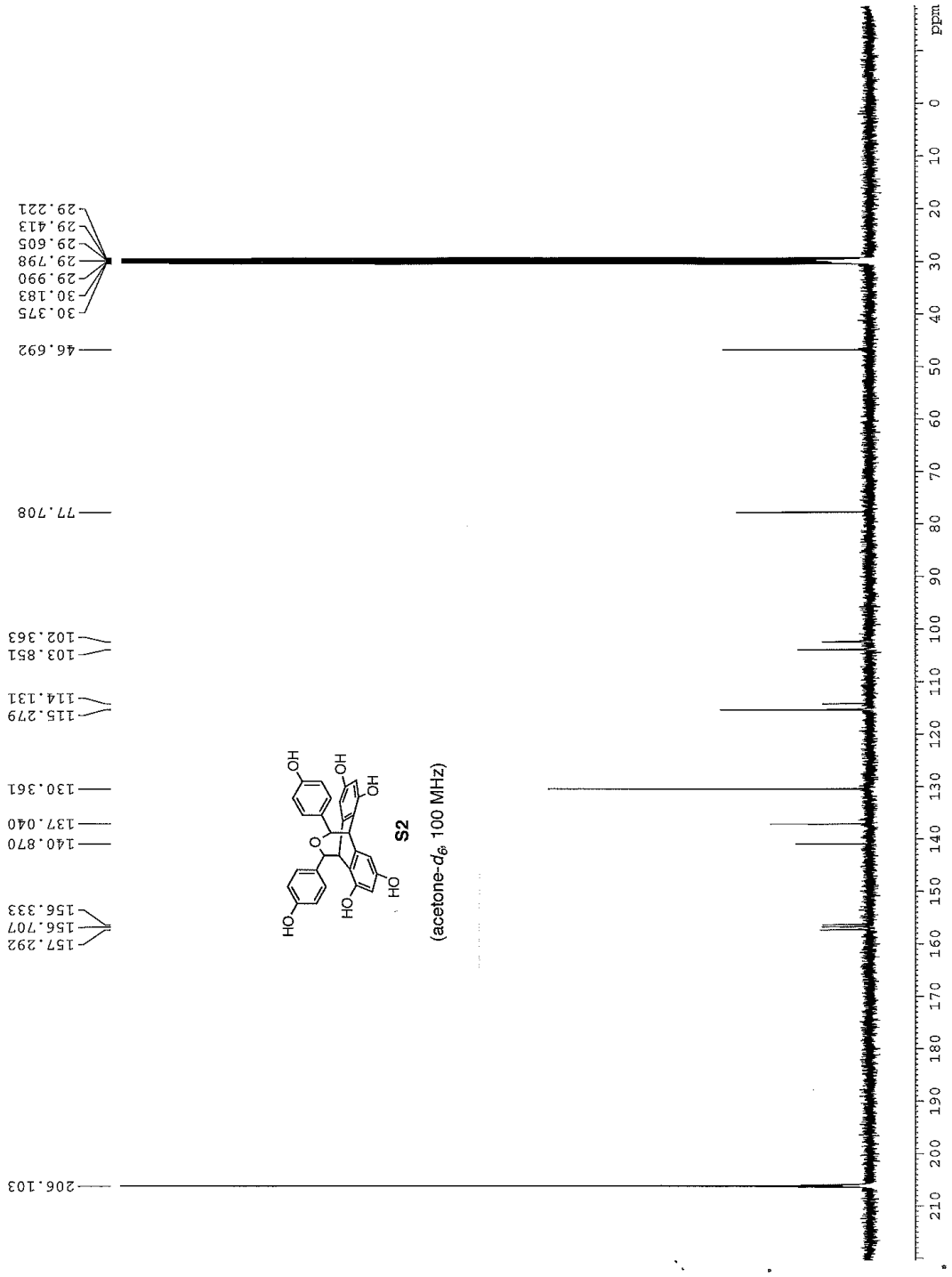
7.793
7.123
7.102
6.711
6.689
6.447
6.442
6.197
6.192
4.943
4.065
2.855
2.825
2.061
2.055
2.050
2.045
2.039
S2
(acetone-d_6, 400 MHz)
ppm
0.99
1.00
1.00
1.00
2.13
2.05
0.66
0.66
0.68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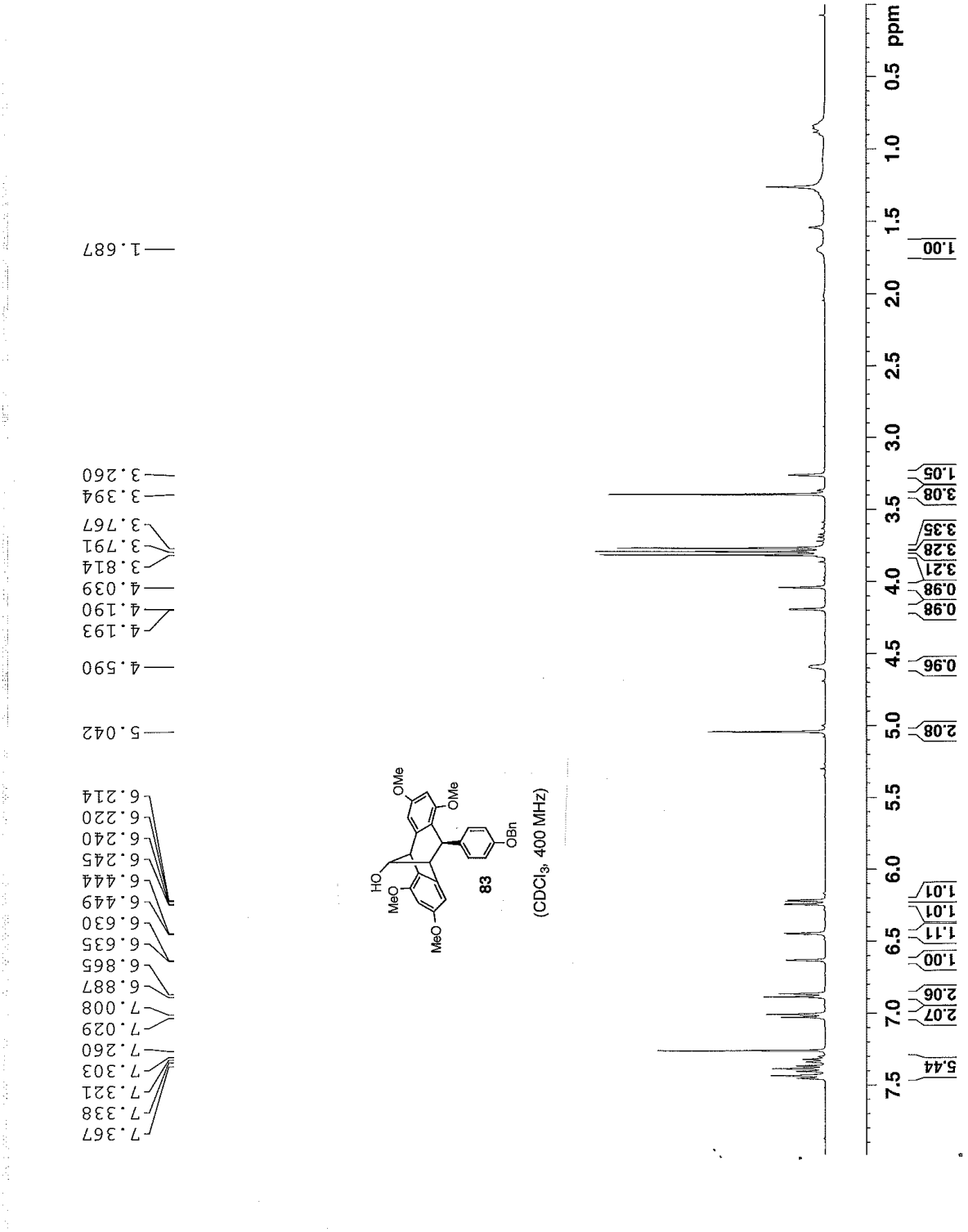
157.292
156.707
156.333
140.870
137.040
130.361
115.279
114.131
103.851
102.363
77.708
46.692
30.375
30.183
29.990
29.798
29.605
29.413
29.221
ppm
S2
(acetone-d_6, 100 MHz)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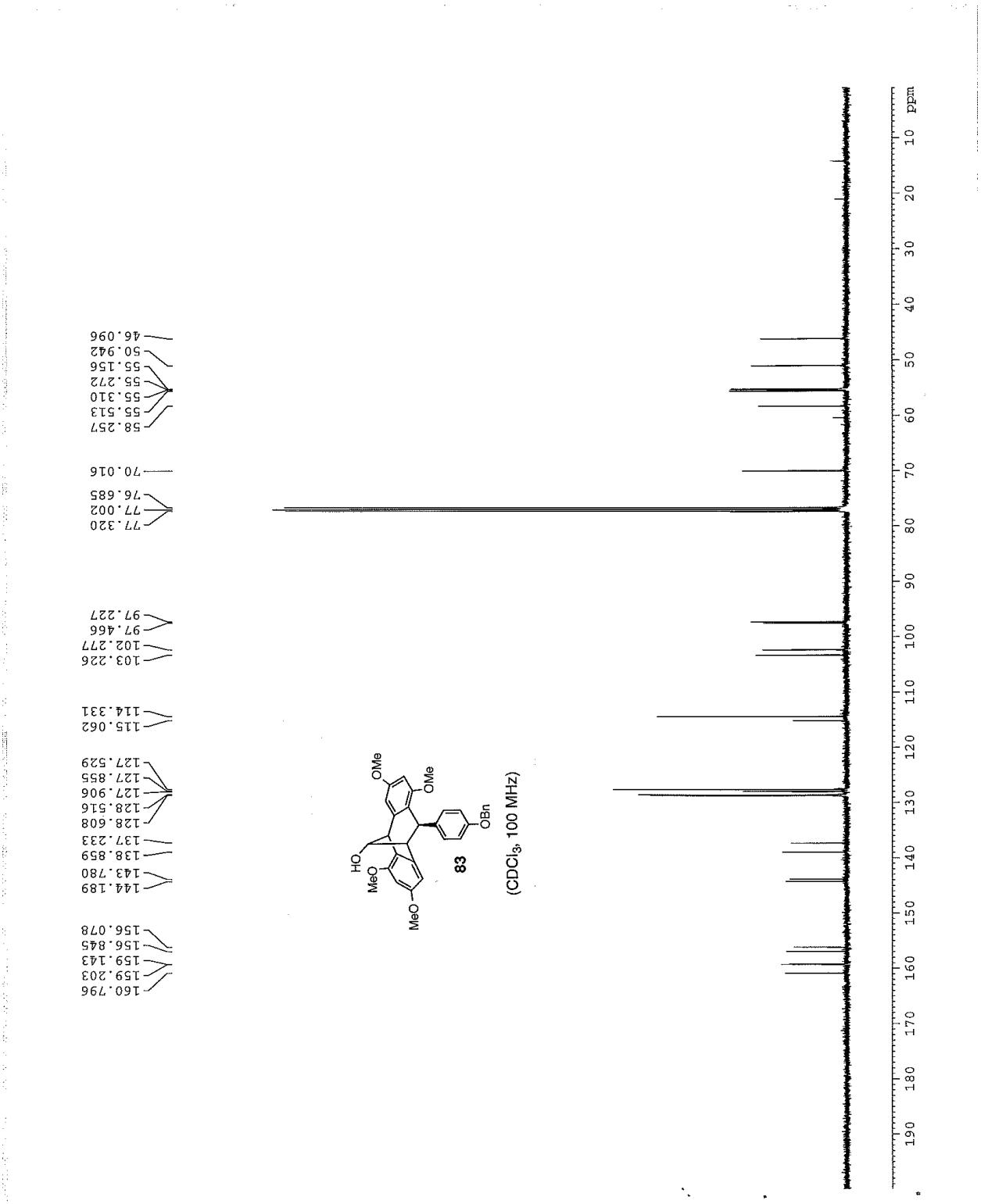
7.338
7.321
7.303
7.260
7.029
7.008
6.887
6.865
6.635
6.630
6.449
6.444
6.245
6.240
6.220
6.214
5.042
4.590
4.193
4.190
4.039
3.814
3.791
3.767
3.394
3.260
1.687
OMe
OMe
OBn
HO
MeO
MeO
83
(CDCl3, 400 MHz)
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
5.44
2.07
2.06
1.00
1.11
1.01
1.01
1.01
2.08
0.96
0.98
0.98
3.21
3.28
3.35
3.08
1.05
1.00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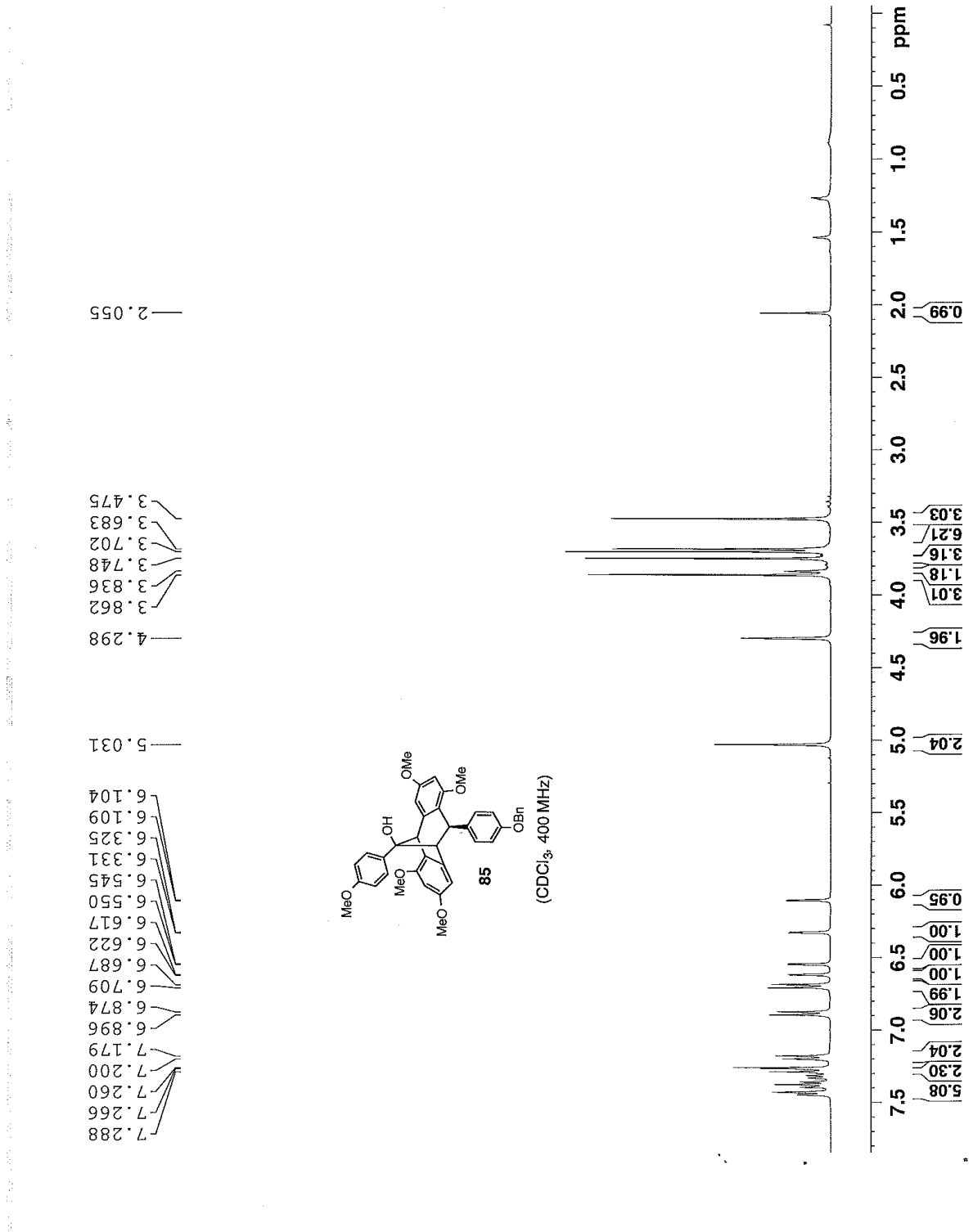
156.845
156.078
144.189
143.780
138.859
137.233
128.608
128.516
127.906
127.855
127.529
115.062
114.331
103.226
102.277
97.466
97.227
77.320
77.002
76.685
70.016
58.257
55.513
55.310
55.272
55.156
50.942
46.096
OMe
OMe
OBn
HO
MeO
MeO
83
(CDCl3, 100 MHz)
ppm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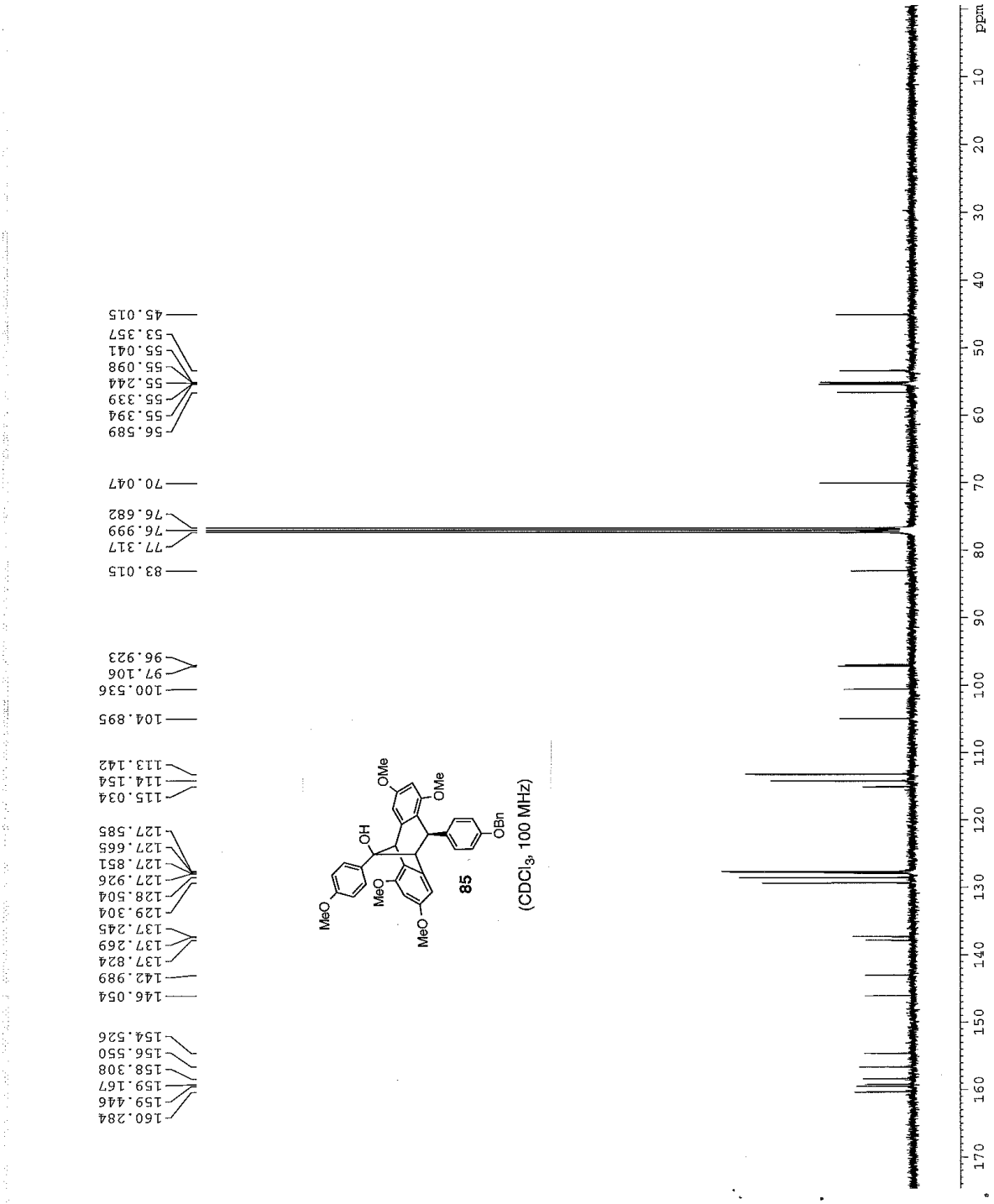
7.266
7.260
7.200
7.179
6.896
6.874
6.709
6.687
6.622
6.617
6.550
6.545
6.331
6.325
6.109
6.104
5.031
4.298
3.862
3.836
3.748
3.702
3.683
3.475
2.055
OMe
OMe
OH
OBn
MeO
MeO
MeO
85
(CDCl3, 400 MHz)
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
5.08
2.30
2.04
2.06
1.99
1.00
1.00
1.00
0.95
2.04
1.96
3.01
1.18
3.16
6.21
3.03
0.99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154.526
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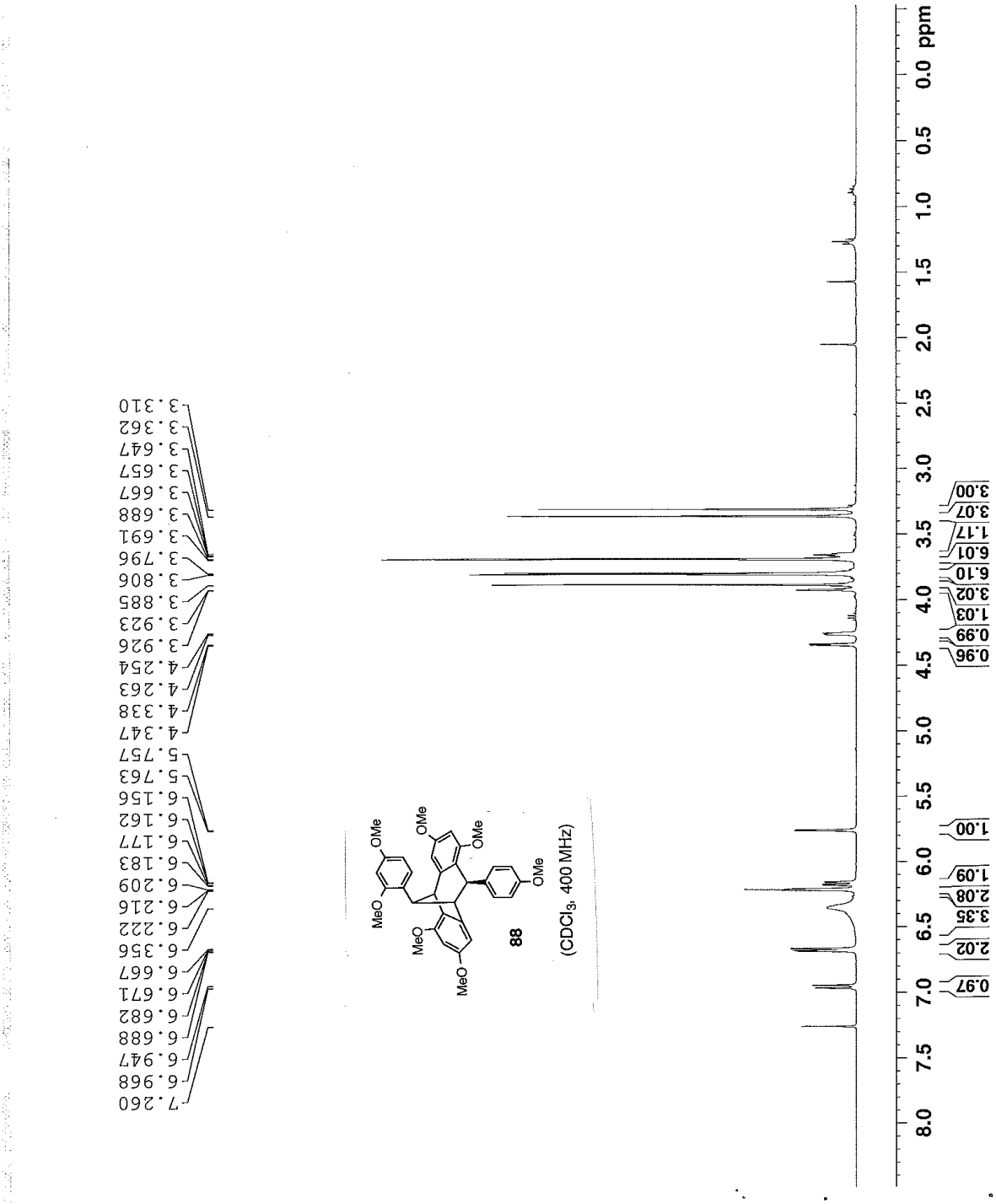
142.989
137.824
137.269
137.245
129.304
128.504
127.926
127.851
127.665
127.585
115.034
114.154
113.142
104.895
100.536
97.106
96.923
83.015
77.317
76.999
76.682
70.047
56.589
55.394
55.339
55.244
55.098
55.041
53.357
45.015
OMe
OMe
OBn
OH
MeO
MeO
MeO
85
(CDCl3, 100 MHz)
ppm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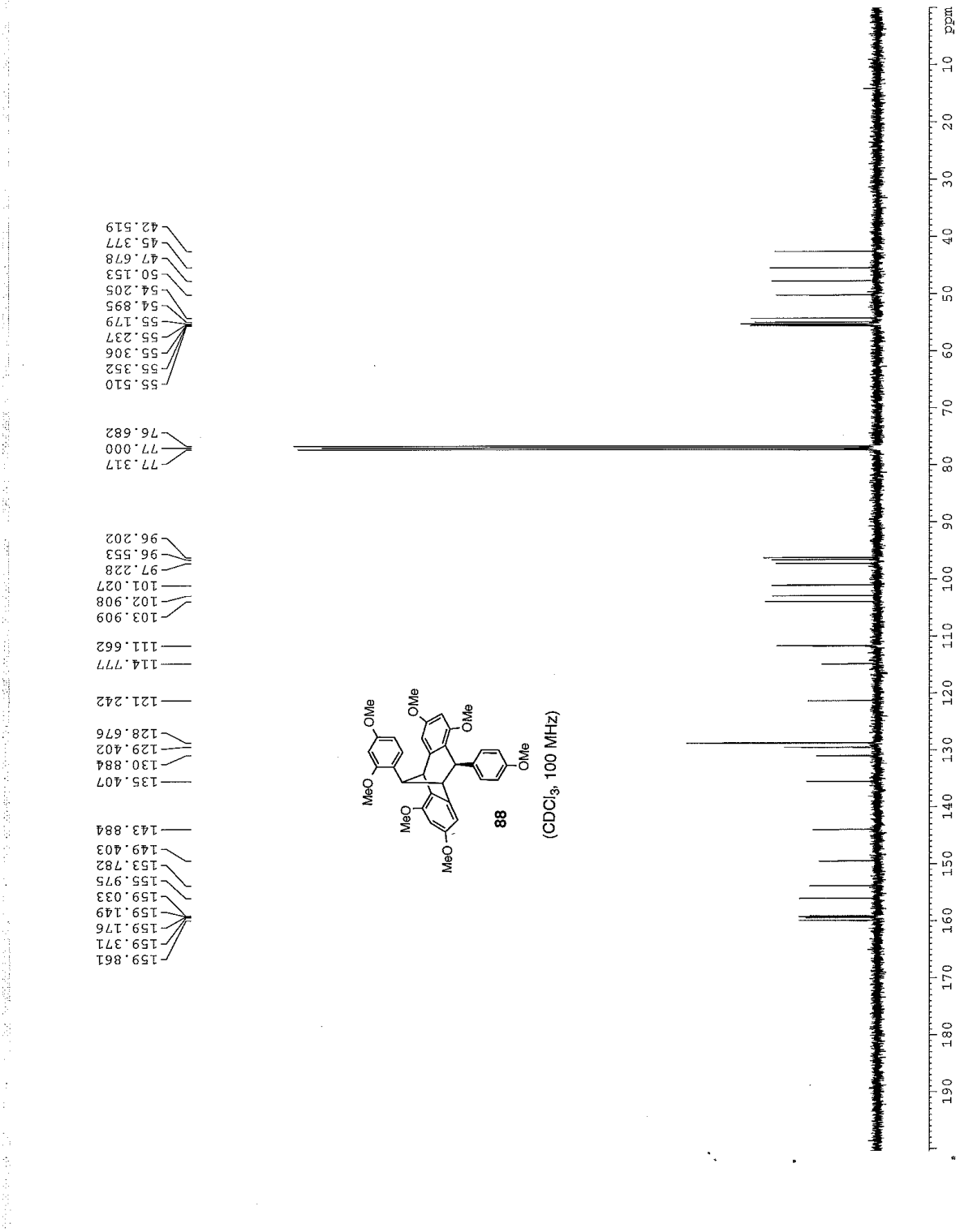
6.947
6.688
6.682
6.671
6.667
6.356
6.222
6.216
6.209
6.183
6.177
6.162
6.156
5.763
5.757
4.347
4.338
4.263
4.254
3.926
3.923
3.885
3.806
3.796
3.691
3.688
3.667
3.657
3.647
3.362
3.310
OMe
OMe
OMe
OMe
MeO
MeO
MeO
88
(CDCl3, 400 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm
0.96
0.99
1.03
3.02
6.10
6.01
1.17
3.07
3.00
1.00
1.09
2.08
3.35
2.02
0.97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153.782
149.403
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135.407
130.884
129.402
128.676
121.242
114.777
111.662
103.909
102.908
101.027
97.228
96.553
96.202
77.317
77.000
76.682
55.510
55.352
55.306
55.237
55.179
54.895
54.205
50.153
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OMe
OMe
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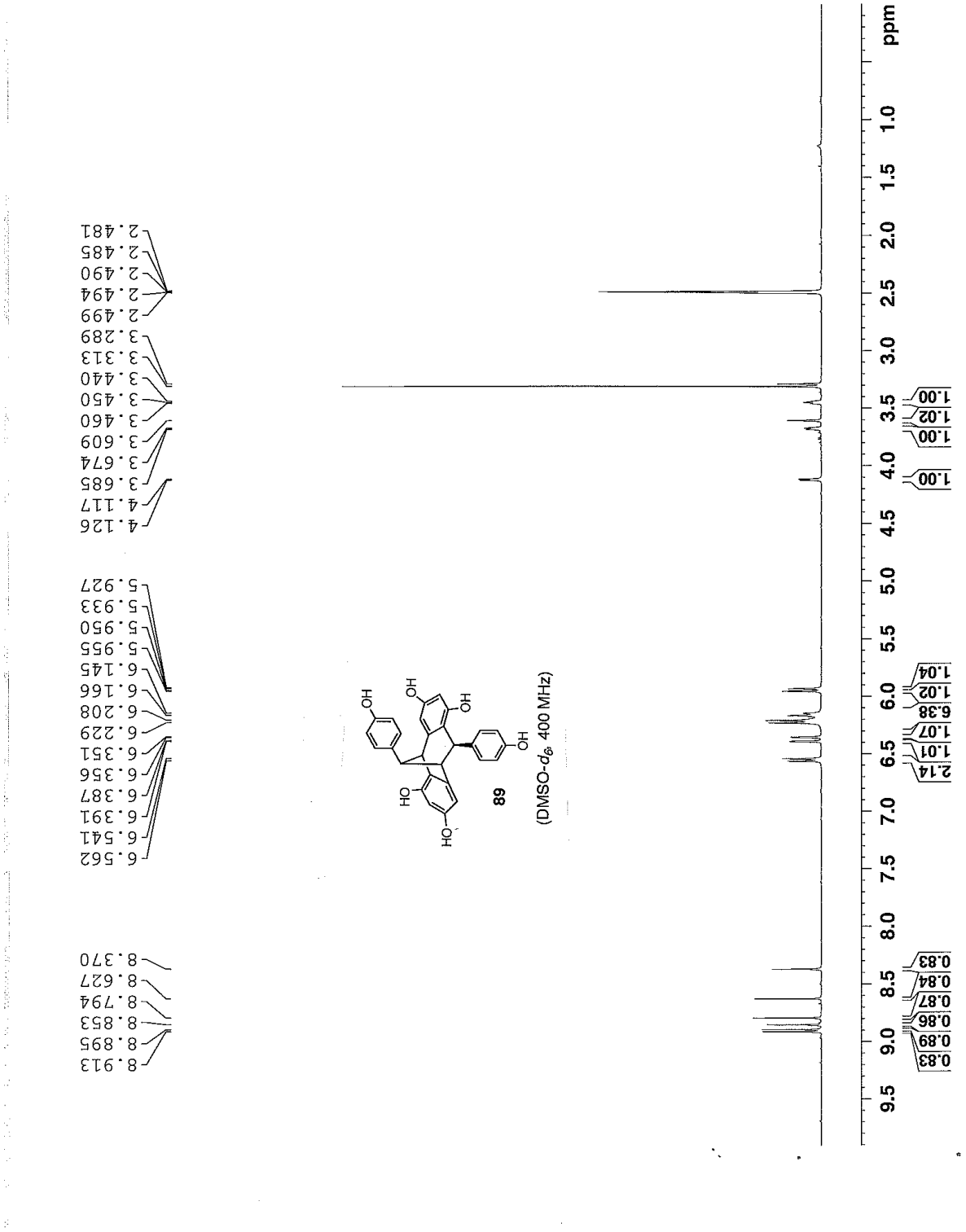
MeO
MeO
MeO
88
(CDCl3, 100 MHz)
ppm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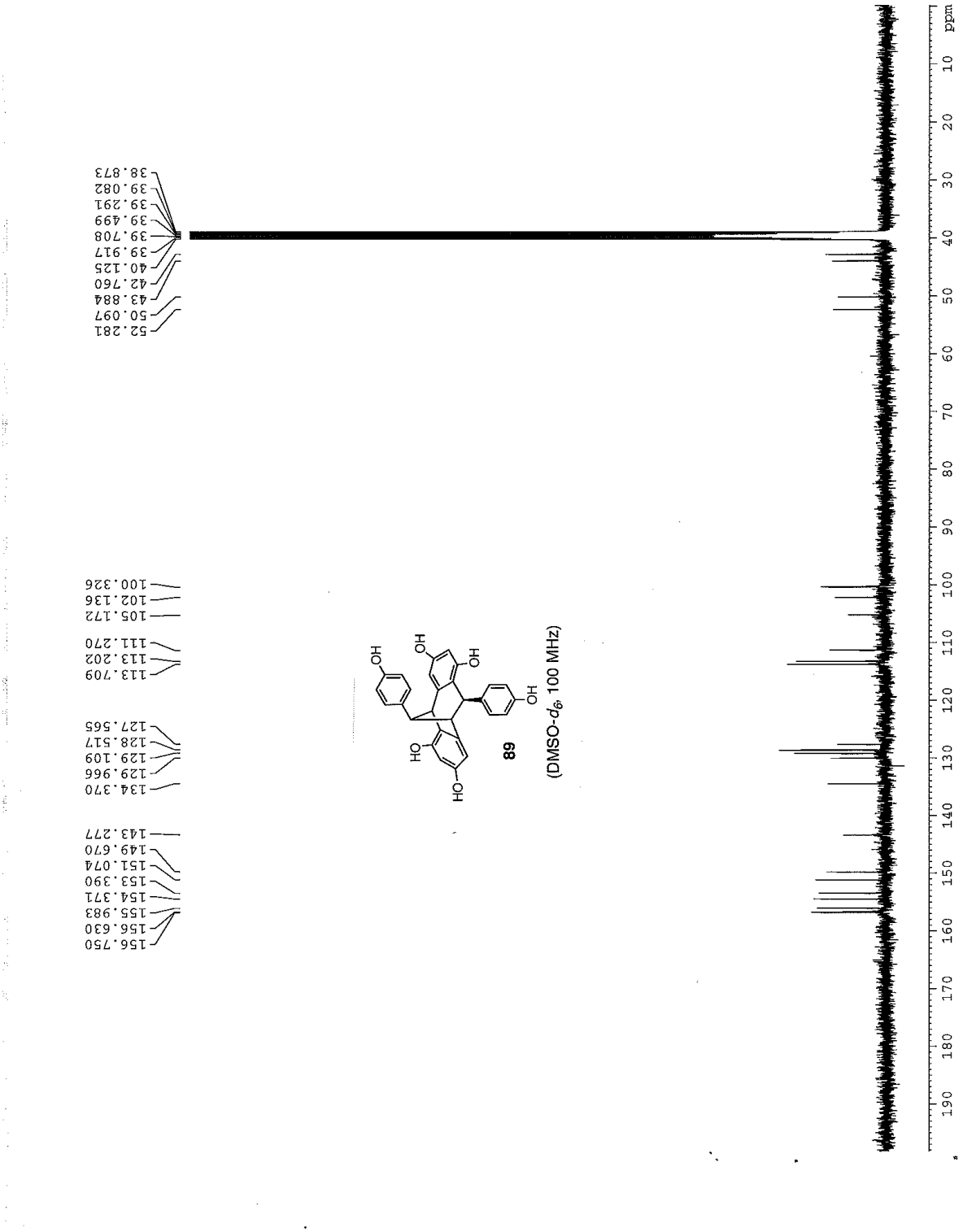
8.895
8.853
8.794
8.627
8.370
6.562
6.541
6.391
6.387
6.356
6.351
6.229
6.208
6.166
6.145
5.955
5.950
5.933
5.927
4.126
4.117
3.685
3.674
3.609
3.460
3.450
3.440
3.313
3.289
2.499
2.494
2.490
2.485
2.481
89
(DMSO-d_6, 400 MHz)
ppm
0.83
0.89
0.86
0.87
0.84
0.83
2.14
1.01
1.07
6.38
1.02
1.04
1.00
1.00
1.02
1.00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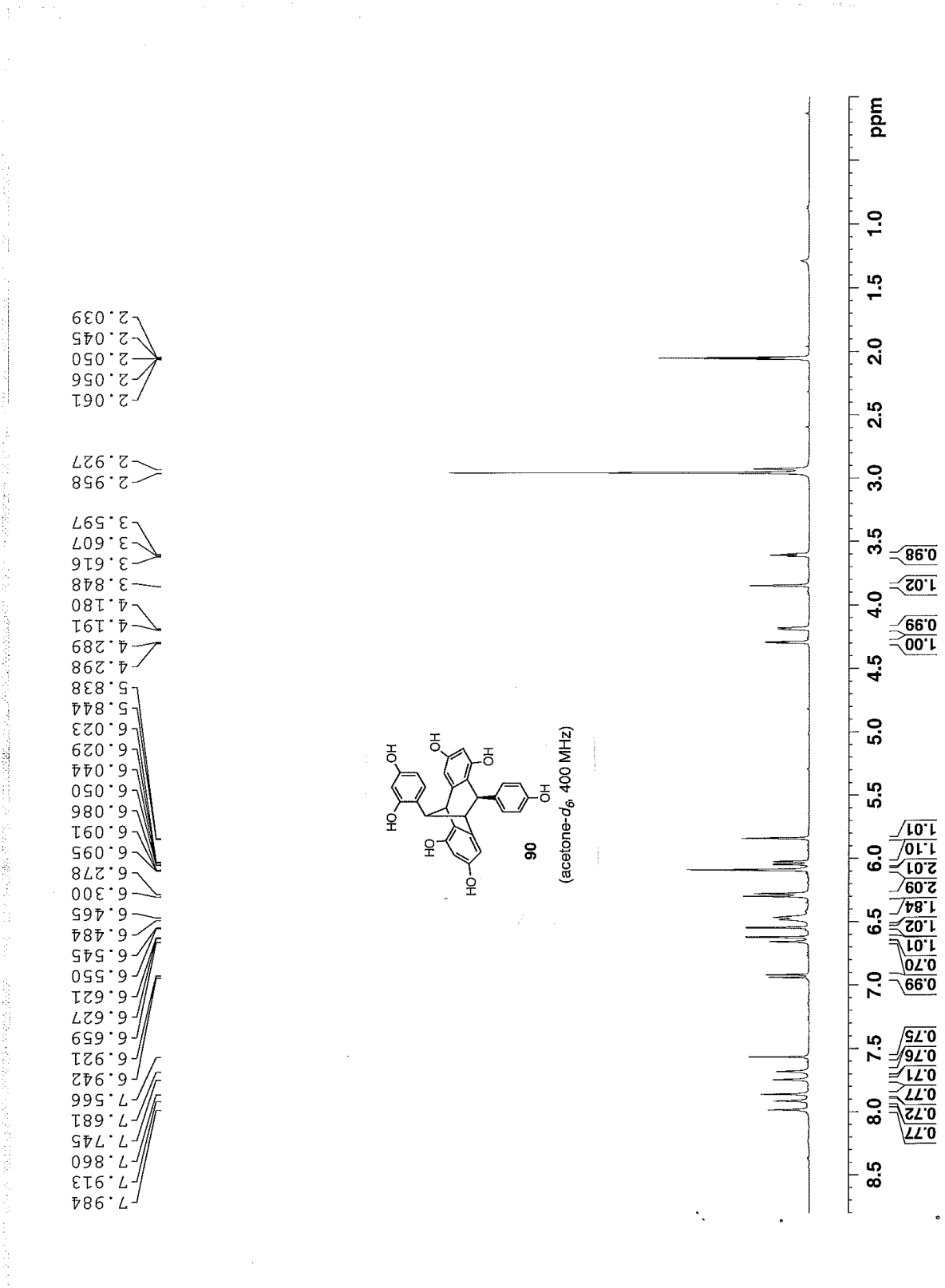
39.499
39.708
39.917
40.125
42.760
43.884
50.097
52.281
100.326
102.136
105.172
111.270
113.202
113.709
127.565
128.517
129.109
129.966
134.370
143.277
149.670
151.074
153.390
154.371
155.983
156.630
156.750
OH
OH
OH
HO
HO
89
(DMSO-d_6, 100 MHz)
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190


90
(acetone-d_6, 400 MHz)
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6.0
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4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.77
0.72
0.77
0.71
0.76
0.75
0.99
0.70
1.01
1.02
1.84
2.09
2.01
1.10
1.01
1.00
0.99
1.02
0.98
7.984
7.913
7.860
7.745
7.681
7.566
6.942
6.921
6.659
6.627
6.621
6.550
6.545
6.484
6.465
6.300
6.278
6.095
6.091
6.086
6.050
6.044
6.029
6.023
5.844
5.838
4.298
4.289
4.191
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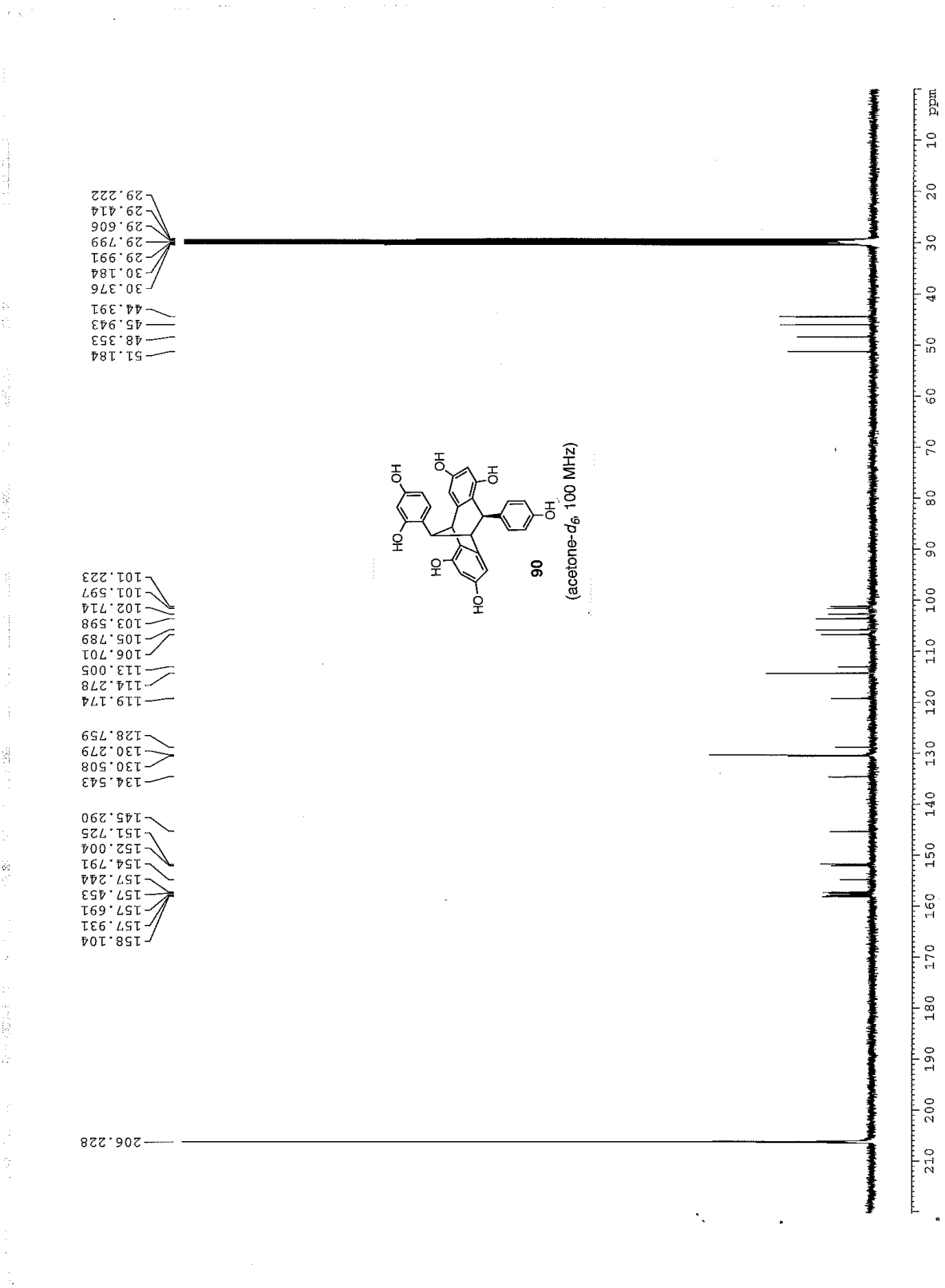
2.958
2.927
2.061
2.056
2.050
2.045
2.039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157.453
157.244
154.791
152.004
151.725
145.290
134.543
130.508
130.279
128.759
119.174
114.278
113.005
106.701
105.789
103.598
102.714
101.597
101.223
51.184
48.353
45.943
44.391
30.376
30.184
29.991
29.799
29.606
29.414
29.222
OH
HO
90
(acetone-d_6, 100 MHz)
ppm

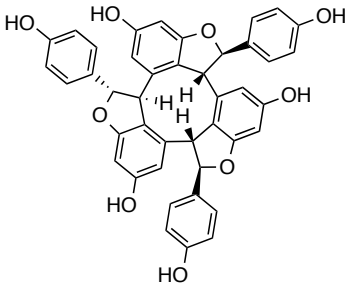
Chapter 3

Explorations Into the Construction of Nine Membered Carbocycles: The Total Synthesis of Caraphenol A

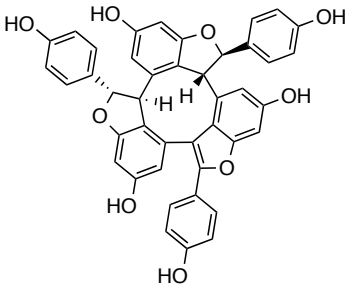
3.1 Isolation and Structure Determination of Nine Membered Ring Containing Resveratrol Based Oligomers.

While many carbon frameworks within the resveratrol class of oligomers at the trimer level, and often higher, can be structurally traced directly back to a precursor dimeric core, there are select architectures unique to the trimer level. One such subclass in the resveratrol family is that of the natural products drawn in Figure 1.[1] The conserved structural feature of this collection is a central, all-carbon nine membered ring core with alternating fused aromatic rings. While this general core motif has found application in various other subfields of chemistry, some of which will be discussed in Chapter 4, to the best of our knowledge the natural products shown in Figure 1 are the only isolated and characterized materials from Nature with such a structure. The first member of this subclass to be described was α-viniferin (1) as outlined in 1977 by Langcake and Pryce.[1a] Aside from the tetramer miyabenol B (**12**),[1k] the product of a single resveratrol addition onto α-viniferin, no other natural products containing this nine membered ring substructure were isolated prior to the 2000-2010 decade when **2**-**11** were all discovered and fully characterized. Given the timeframe with regard to methods of structural elucidation, and the lack of precedent for such a compound in Nature, the accurate identification of the structure of α-viniferin in 1977 is actually quite remarkable. Aside from IR and UV spectra, which merely confirmed the presence of "unconjugated phenolic chromophores," the structure was determined entirely from ^{1}H NMR spectra and mass spectrometry, with insufficient material to obtain a useful ^{13}C NMR spectrum. Through methylation they determined the presence of six free phenols and that, in conjunction with the mass spectrometry data, indicated the existence of four additional rings, apart from the six aromatic rings, and three phenol ether moieties. The co-isolation with resveratrol and ε-viniferin (Figure 4, Chapter 1) indicated that this compound was likely an oligomer of resveratrol and ^{1}H NMR spectrum showed the phenol substitution pattern

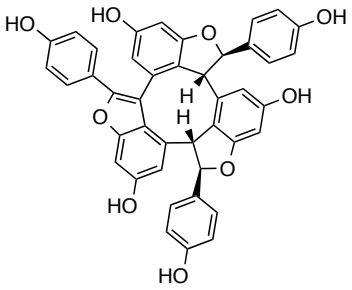
Figure 1. 9-Membered Ring Containing Resveratrol Oligomers



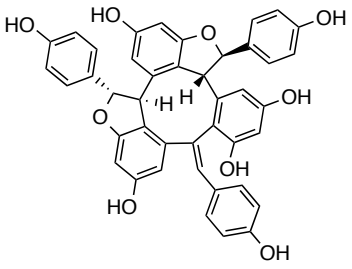
1: α-viniferin



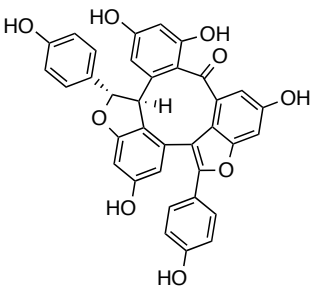
2: caraphenol A



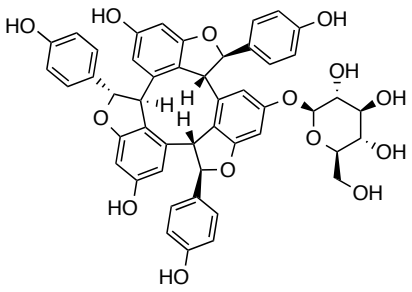
3: sophorastilbene A



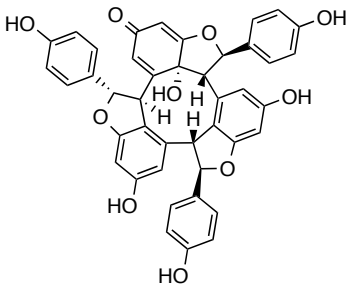
4: caragaphenol A



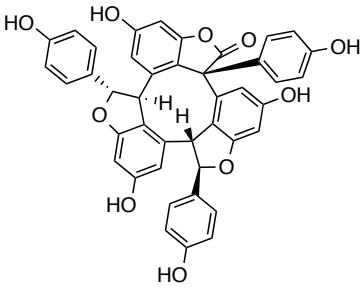
5: carasiphenol D



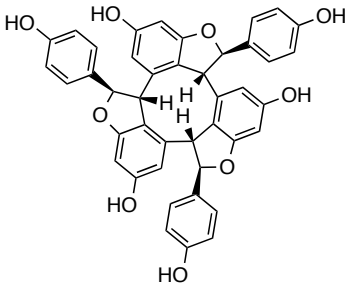
6: α-viniferin 13b-*O*-β-glucopyranoside



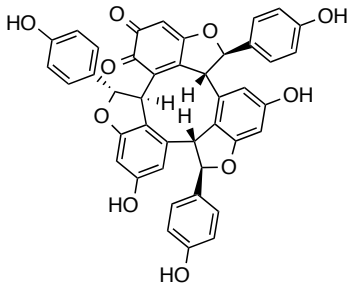
7: grandiphenol C



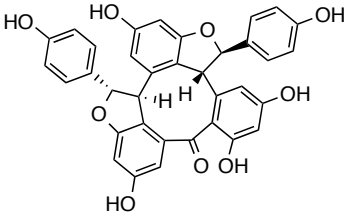
8: grandiphenol D



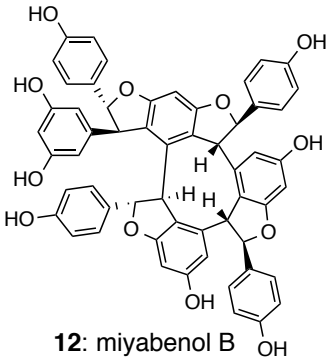
9: curcusinol



10: hopeanolin



11: hopeachinol B



12: miyabenol B

to be consistent with resveratrol units. Lastly, the authors noted the presence of three pairs of viscinal methine protons. Taking into account the relative shifts of these proton signals and the other data gathered, the conclusion was drawn that they must belong to 2,3-dihydrobenzyfuran rings as was already shown to be present in the natural products ε-viniferin and hopeaphenol. These adjacent protons were believed to be in a *trans* relationship assuming homology to the previously isolated natural products, although the authors do note that there is ambiguity here given that the precedent for the coupling constants of such protons to be unpredictable. The absence of C_{3v} symmetry then indicated the relative stereochemistry among the three dihydrobenzofuran units to be "*trans-cisoid-trans-transoid-trans*" as drawn in Figure 1. Following this seminal structure determination, other members of the subclass were characterized by various 2D-NMR methods as well as homology to the originally isolated α-viniferin. No X-ray crystallography of these materials, or their derivatives, have been reported.

Regarding the plant sources from which these natural products have been extracted the variety is also great. While the more recently identified family members have only been obtained from one or two specific plant sources, the early identification of α-viniferin has led to its recognition in the extracts of approximately 27 plant species across 12 genera. As discussed in Chapter 1, the highest prevalence of these, and any other resveratrol-based natural product, is in infected and/or damaged plant tissue, often induced in the isolation process to increase the overall yield of those natural products. Within the plant constituents themselves, the bark, stem, roots, and leaves have served as the sources of these materials, although the latter is more rare.[1] In conjunction with the majority of isolation efforts described has been the identification of an exciting array of bioactivity, as will be discussed in more detail in the next section.

3.2 Bioactivity of Nine Membered Ring Containing Resveratrol Oligomers

Not surprisingly, the isolation of α-viniferin (**1**) more than 20 years prior to that of most other family members (**2**-**12**) has led not only to its identification among a great variety of plant sources, but also its submission to numerous bioactivity assays. While the other nine membered ring containing natural products have also undergone limited testing, the majority of the bioactivity discussed will be in reference to α-viniferin. We note here that part of our goal in synthesizing members of this resveratrol oligomer subclass was to eventually submit them to the same level of biological evaluation as α-viniferin. Given the highly similar nature of the frameworks with respect to three-dimensional structure, this exercise may prove useful in identifying the structural components responsible for some of this exciting bioactivity. The reports discussed below will be organized according to the disease area to which they apply.

A great deal of research effort had been dedicated to the search for effective treatments of Alzheimer's disease.[2] Of the potential therapeutic pathways identified for treatment, acetylcholinesterase inhibition has come forth as an exciting and well-pursued avenue[3] since acetylcholine is a critical neurotransmitter and the cholinergic system is known to be highly involved in memory processing. Theoretically, by inhibiting the degradation of this molecule in the brain through blocking the action of acetylcholinesterase, the effects of cholinergic transmission would be increased, thus improving cognitive function. With this in mind, Sung *et al.* submitted a number of compounds to an acetylcholinesterase biassay and identified α-viniferin as a potent inhibitor (IC_{50} = 2.0 μM).[4] Furthermore they showed the inhibition to be specific, reversible, and non-competitive. As compared to other investigated therapies, α-viniferin showed excellent selectivity for acetylcholinesterase over the related butylcholinesterase. Later studies revealed that caraphenol A (**2**) also showed potent inhibition

of the same enzyme (IC_{50} = 11.7 μM).[5] While relatively little is known about the human 5-hydroxytryptamine receptor 6 (5-HT_6) receptor, initial studies have revealed its involvement in cognitive disorders, including Alzheimer's disease, with α-viniferin also being shown as a potent inhibitor of it as well (IC_{50} = 2.0 μM).[6] Given the understanding yet to be obtained for this receptor, α-viniferin may serve as a valuable probe of its function and activity, if not a therapy itself.

Outside of this area, inflammatory diseases have also received, and continue to receive, the attention of the research community as it searches for new and improved therapies. In independently verified assays, α-viniferin has been shown to have encouraging anti-inflammatory activity in the context of carrageenin-induced paw edema and adjuvant-induced arthritis in mice models.[7,8] A later study confirmed that this inhibition was achieved in a dose-dependent manner. Through careful analysis of the pathways leading to such beneficial phenotypes, evidence was gathered to support the theory that α-viniferin induces these effects by preventing the upstream phosphorylation of the STAT-1 gene, which in turn reduces the expression of certain inflammatory genes activated by STAT-1.[9] With a greater understanding of this pathway and the role of α-viniferin, it is hoped that clinically useful treatments may be developed.

Though there are a number of other bioactive assays from which α-viniferin has drawn exciting results, the last to be discussed in the context of this writing will be that of anti-cancer properties. Both α-viniferin (**1**) and sophorastilbene (**2**) have shown cytotoxicity in a number of cancer cell lines. Chowdhury *et al.* in their investigations of stilbene polyphenols and flavonoids show not only that these two natural products show potent cytotoxicity, but their activity has the highest tumor specificity among those compounds tested.[10] While cytotoxicity is perhaps the

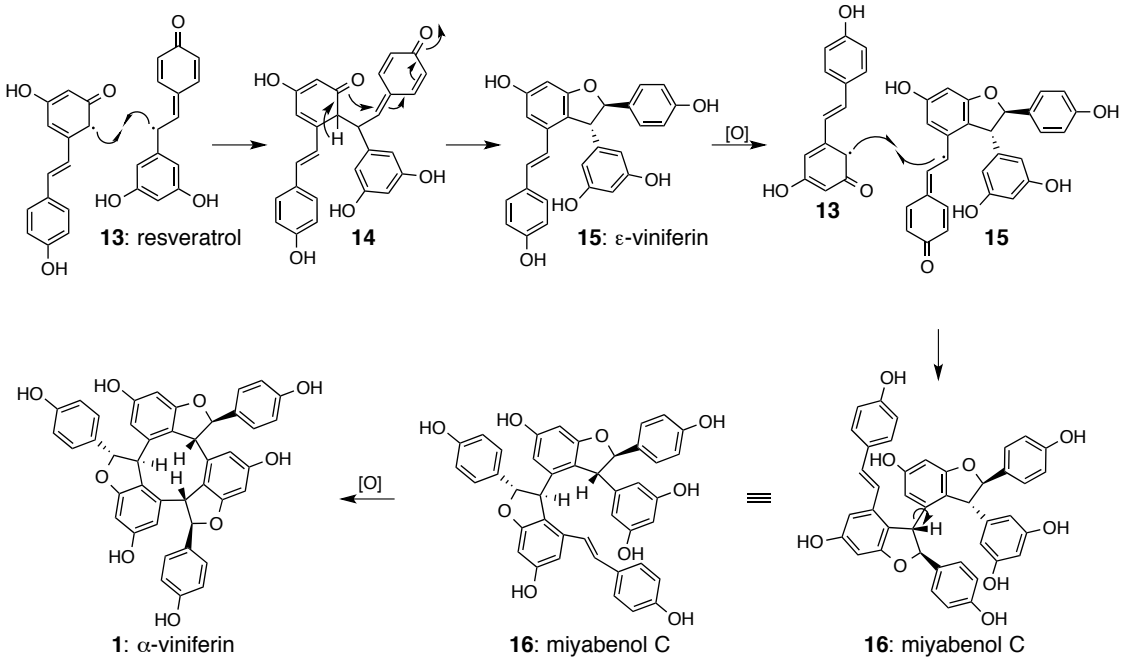
most direct method for evaluating the potency of a compound for treating cancer, other modes of action to reach such an end have been elucidated. The multidrug-resistance protein-1 (MRP1) is a membrane protein often expressed in tumor cells taht acts as an efflux pump transporting drugs and other compounds outside of the tumor cell.[11] MRP1 is particularly expressed in those cancer types exhibiting high resistance to drug therapy with the active compounds effectively being removed from the cancer cell before initiating their cytotoxic effect. α-viniferin and sophorastilbene A were both found to be potent inhibitors of MRP1 (0.8 μM and 3.5 μM, respectively).[12] By obtaining a greater comprehension of this protein and developing effective therapeutics to inhibit it, drug resistance in numerous cancer types can be suppressed, thus increasing the effectiveness of current drug treatments. The intriguing bioactivity of α-viniferin discussed above and the potential to investigate similar bioactivity in the additional natural products shown in Figure 1 played no small part in our choosing to pursue them as synthetic targets.

3.3 Biosynthesis of Nine Membered Ring Containing Resveratrol Based Natural Products

Much like heimiol A and hopeahainol D (Chapter 2), little relevant biosynthetic hypotheses of any nine membered ring containing resveratrol oligomer have been published. The presence of co-isolates in concert with the generally accepted notion of oxidative, radical-based resveratrol oligomerizations lends itself to a reasonable biosynthetic proposal outlined below in Scheme 1. As before (See Scheme 1, Chapter 2), we begin with the biosynthesis of ε-viniferin (**15**) from resveratrol (**13**). Following its construction from two units of resveratrol (**13**), we believe ε-viniferin (**15**) oxidatively couples with resveratrol by the shown mechanism to

produce a new, trimeric natural product in the form of miyabenol C (**16**).[1k] This particular step has been previously put forth by Romeo as a likely pathway to miyabenol C (**16**).[13] While **16** is

Scheme 1. Biosynthesis of α-viniferin.

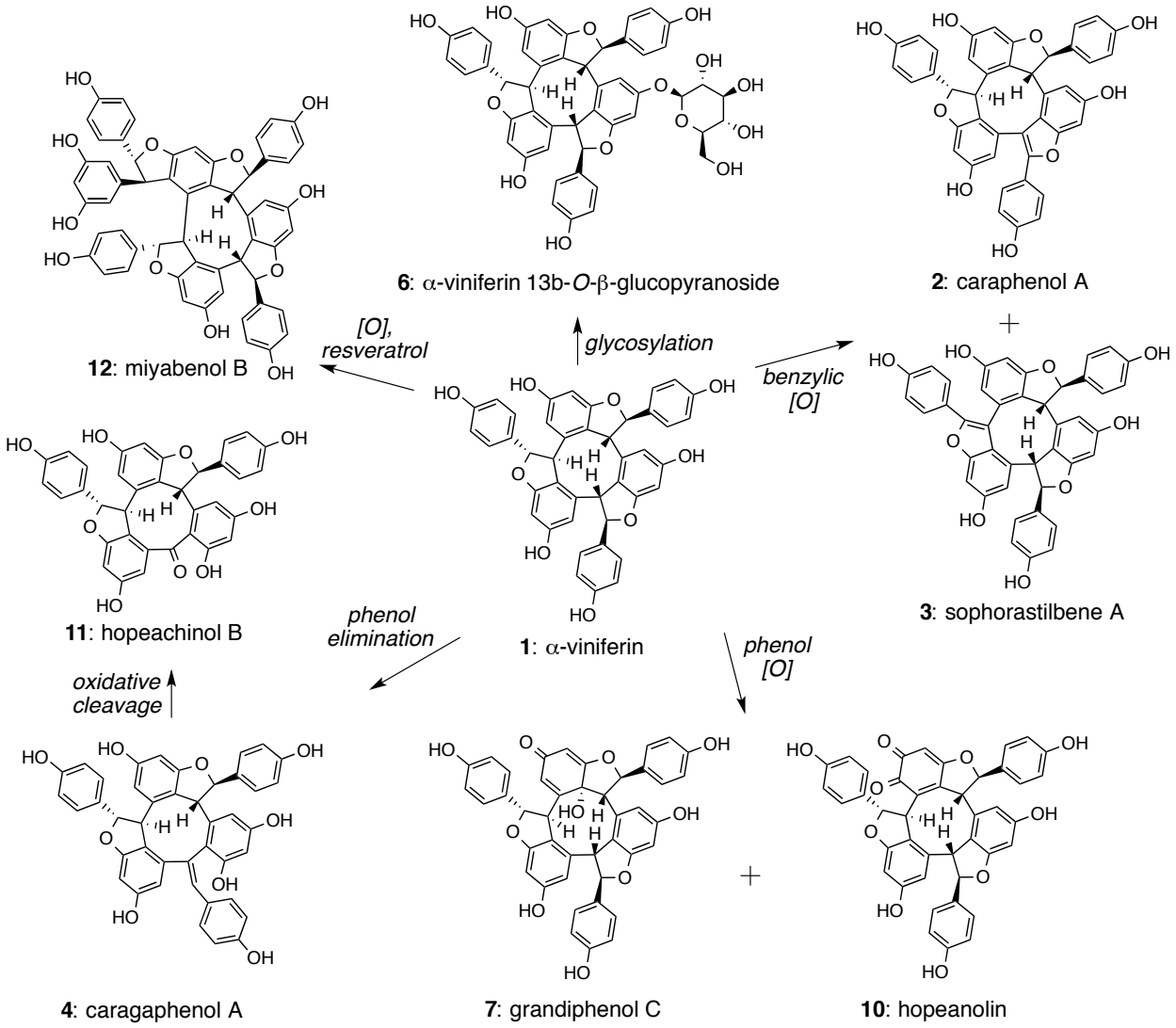


generally drawn by isolation chemists as shown first in Scheme 1, the alternate drawing below it suggests it to be a potential precursor of α-viniferin (**1**), primed for such a synthesis through additional oxidation. This theory has been put forth specifically by the Iinuma group in 2009, who published it along with their isolation of grandiphenol C and D (**7** and **8**).[1g] It was thus proposed that oxidative cyclization of miyabenol C (**16**) delivers α-viniferin (**1**), a notion further supported by their having been isolated together from *Caragana sinica*.[14]

At this point, we propose that further oxidative elaboration likely leads to other members of this subclass, as shown in Scheme 2. Addition of another resveratrol unit can take place by similar mechanisms to give miyabenol B (**12**),[1l] while straightforward glycosylation would lead to α-viniferin-13b-*O*-β-glucopyranoside (**6**).[1f] Further oxidation of α-viniferin (**1**) itself may come in the form of hopeanolin (**10**)[1i] or caraphenol A (**2**).[1b] Simple internal phenol elimination

of a dihydrobenzofuran unit would afford caragaphenol A (**4**),[1d] material which could then produce hopeachinol B (**11**)[1j] upon oxidative cleavage of its olefin. Grandiphenol D (**8**),[1g] on the

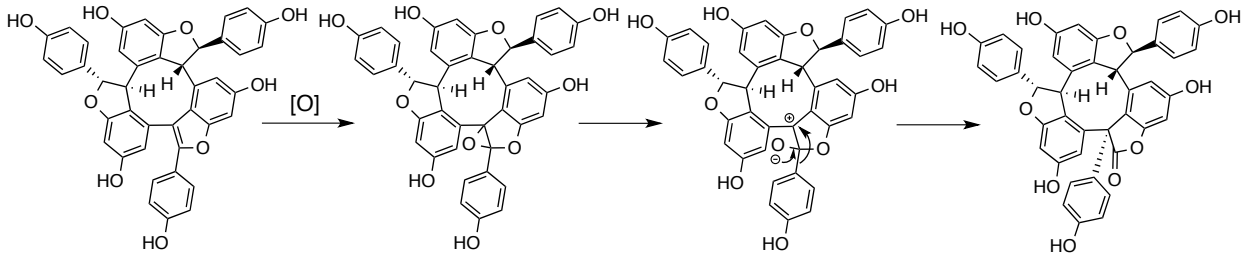
Scheme 2. Proposed Biosynthesis of 9-Membered Ring Containing Resveratrol Oligomers From α-viniferin



other hand, may arise from a more unique mechanism. Epoxidation of the benzofuran in caraphenol A (**2**) would lead to **17** which, through appropriate activation, could then open to **18** and undergo a semi-pinacol rearrangement ultimately delivering grandiphenol D (**8**) as shown in Scheme 3. The isolation chemists set forth a slightly different proposal with their report of the

structure of this natural product, though its elements implement essentially the same principles.[1g] A similar pinacol rearrangement-based hypothesis to furnish the lactone with an alpha quaternary

Scheme 3. Proposed Biosynthesis of Grandiphenol D From Caraphenol A

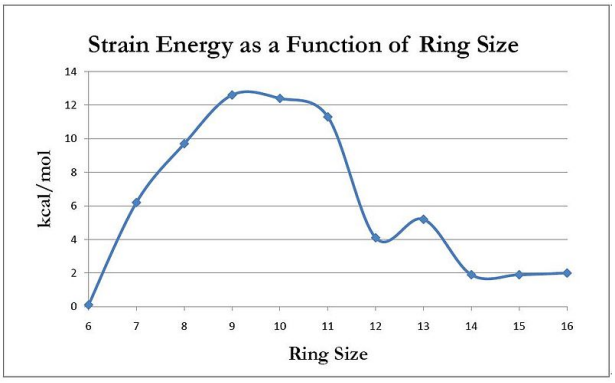


center was proposed in the biosynthesis of hopeahainol A by Snyder *et al.* and later supported experimentally by their synthetic route as noted in Chapter 1.[15] As support for the theoretical genesis of most of the natural products discussed having come from α-viniferin (**1**), it is worth noting that it was isolated alongside, or from the same plant species during a different isolation, with every single compound shown in Figure 1 except curcusinol (**9**) and miyabenol B (**12**). While no nine membered ring co-isolates are reported for curcusinol (**9**), in the isolation of miyabenol B (**12**) the authors propose a slightly alternate pathway in which the fourth resveratrol unit is appended to miyabenol C (**16**) prior to closing the nine membered ring.[1k] While none of these biosynthetic proposals have been rigorously investigated, we believe, along with the authors identified above, that the known oxidative nature of resveratrol oligomerization as well as suggestive co-isolations of related structures circumstantially support these claims as reasonable hypotheses. Whether they would lead to effective syntheses is even harder to discern. Though, as will be discussed, they do afford fodder for designing synthetic sequences for the class.

3.4 Previous Work Towards All-Carbon Nine Membered Rings

No synthetic studies, let alone a total synthesis, of any member of the nine membered ring containing subclass of resveratrol oligomers have been reported to date. While the survey of previous resveratrol oligomer syntheses put forward in Chapter 1 (Section 1.6) does hold relevance here with regard to some of the nuances in constructing polyphenolic natural products, the key challenge of these molecules resides in their central nine membered ring. It is a well-established principle in organic chemistry that medium sized rings (8-12 members, though some include seven and 13-membered rings in this category) are particularly unfavorable and difficult to

Figure 2. Correlation of Ring Strain Energy vs. Ring Size



form as compared to their more standard, and more commonly found, counterparts (five and six membered rings, see Figure 2).[16] While a six membered ring generally has available to it a chair conformation to temper unfavorable interactions among substituent groups, medium-sized rings usually lack such an optimal setting.

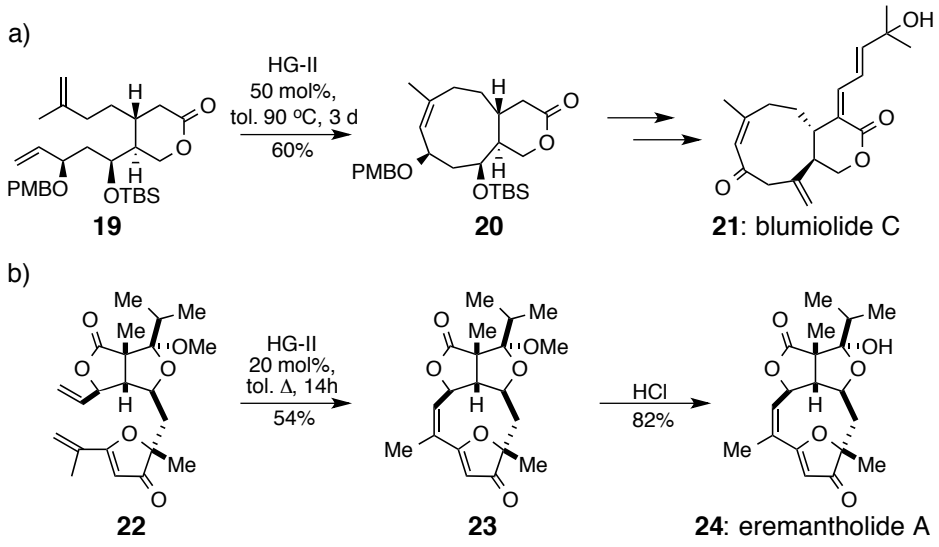
In the quest to forge rings of this type, alternate pathways are commonly favored. It thus falls to the chemist to devise strategies and methods that will favor the desired outcome, often in spite of high kinetic and thermodynamic barriers. Among the possible medium-sized rings are found both carbocycles and heteroatom containing rings. While many methods exist for constructing C-C bonds in the context of a ring-closing event, the options available for

heteroatom bonds (C-O, C-N, C-S) are far greater. The selection of functional group manipulations and nucleophile/electrophile pairs that involve heteroatoms give way to an abundance of strategies for bond formation whereas all-carbon medium sized rings allow fewer methods. Of particular rarity in the literature is the presence of all carbon nine membered rings and as precedent for the primary challenge of this project, the approaches towards their construction will be briefly reviewed, organized into four main categories.

3.4.1 Ring-Closing Metathesis

Few methods developed in the last 50 years compete with olefin metathesis in terms of power in forming C-C bonds (excepting palladium cross-coupling).[17] Among its many applications is that of natural product synthesis, particularly the joining of two terminal olefins to forge a single olefin-containing ring; this process is known as ring-closing metathesis or RCM. The power of this method has been used to forge numerous challenging rings, but, in the context of nine membered ring containing natural products we find few instances of success, with two representative examples shown in Scheme 4. In the first, en route to the diterpene blumiolide C

Scheme 4. Key, Ring-Closing Metathesis in the Total Synthesis of a) Blumiolide C and b) Eremantholide A.



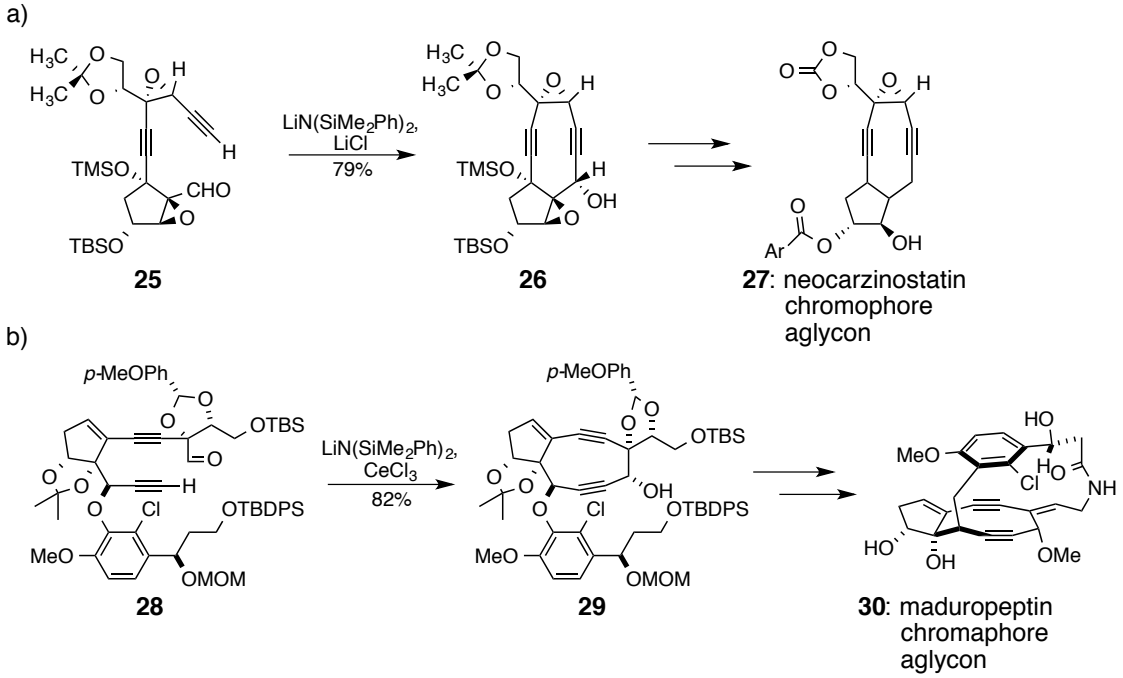
(**21**), the Altmann group needed to identify a way to generate an all-carbon nine membered ring and, given the presence of an internal alkene in that ring, they sought to do so using RCM.[18] As shown, they were successful in converting **19** to **20** in an impressive 60% yield. Unfortunately, the reaction conditions dictated heating at 90 ^{o}C for a period of three days in toluene using 50 mol% of Hoveyda-Grubbs II catalyst (at a cost of >$360/gram). While this approach achieved the desired goal, the drawbacks for its employment are not trivial in terms of cost and time economy. In the second example, drawn in part b of Scheme 4, Li and Hale achieved ring formation of **23** in 54% using the same catalyst, but with lower catalyst loading and reaction time; subsequent conversion of the mixed ketal to a hemiketal using HCl completes the synthesis of eremantholide A (**24**).[19] In terms of broader application to the construction of other nine membered rings, this method would require the ability to elaborate from an internal olefin and while this criteria would be met by a large number of target carbocycles, the relevant substructure for the purposes of this project (see Figure 1), lacks such a feature. Thus, the alternating pattern of fused aromatic rings on the nine membered ring core make it ineligible for direct construction via RCM, excepting an approach that might build an aromatic ring from an alkene through a multistep approach.

3.4.2 Nucleophilic Addition of an Acetylide

A second motif to include an all carbon nine membered ring in a natural product is that of the enediyne. Made famous by its emergence as a tool for DNA cleavage in the context of antibiotics,[20] this substructure is generally found in nine and ten membered rings. Shown above in Scheme 5 are two examples in which this ring has been closed in the context of natural product synthesis. In their report detailing the total synthesis of neocarzinostatin (**27**) in 1996,

Myers *et al.* constructed precursor **25** and, through simple acetylide generation using strong base, were able to add it into the appropriate aldehyde to furnish **26** in 79% yield.[21] Though missing the "ene" portion of an endiyne, a similar example is seen in the 2007 total synthesis of the

Scheme 5. Key Acetylide Addition Into an Aldehyde in the Total Synthesis of a) Neocarzinostatin Chromaphore Aglycon and b) Maduropeptin Chromaphore Aglycon.

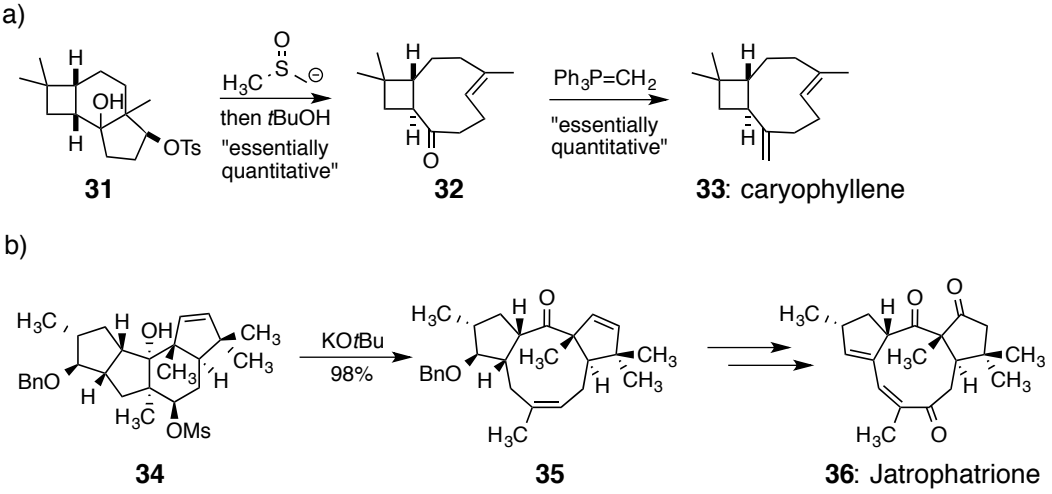


maduropeptin chromophore aglycon (**30**) by the Hirama group which proceeded in >82% yield for the key conversion of **28** to **29**.[22] Other related instances of this technique are also found in the literature.[23] The presence of two alkyne moieties in both of the above described substrates serves to mediate some of the unfavorable interactions that discourage medium-sized ring formation as it removes substituents from four of the nine involved carbon atoms and, presumably to the benefit of the desired pathway, limits rotational freedom of three bonds in the cyclization precursor. While this method of acetylide addition effectively accomplishes ring formation in some instances, a minimum of one alkyne is required, which again disqualifies our system of interest from any direct and/or obvious application.

3.4.3 Grob Fragmentation

A general, and historically successful, strategy for the construction of challenging substrates is to devise a method for transferring the knowledge and synthetic technology developed for a simple motif into a difficult one. Such applies to the Grob fragmentation,[24] wherein chemists have synthesized challenging medium sized rings by first creating much simpler 5,6- and 6,6-fused bicyclic frameworks, for which there are numerous strategies and methods, and effectively opening them up through cleavage of the central, transannular bond. This approach is outlined in two examples below in the context of terpenes (Scheme 6). In the first, Corey's synthesis of caryophyllene (**33**) published in 1964, these researchers produced tricyclic framework **31** through known methodology and then induced a Grob fragmentation to

Scheme 6. Key Grob Fragmentation in the Total Synthesis of a) Caryophyllene and b) Jatrophatrione.



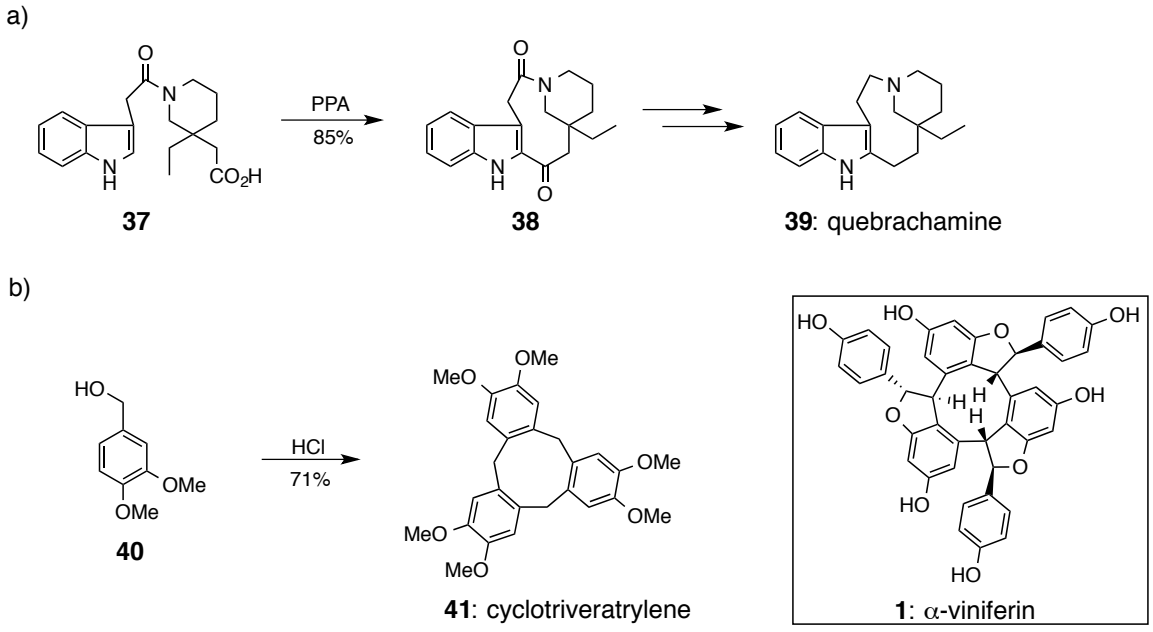
accomplish the formation of the requisite nine membered ring **32** in an impressive, nearly quantitative yield with its *trans*-olefin as dictated by the stereochemistry of the preceding tosylate (Scheme 6a).[25] Nearly 40 years later, Paquette *et al.* constructed the central ring of jatrophatrione (**36**) through a similar approach from precursor **34** to give tricyclic **35** in 98% yield as shown in Scheme 6b.[26] Thus, with an appropriately designed substrate, this method

represents a powerful approach for medium-sized ring synthesis, particularly for nine and ten membered rings. Unfortunately, it requires vicinal sp^3-hybridized carbons to accommodate elimination of the leaving group (usually -OTs or OMs), a feature which once again renders this method inapplicable to our nine membered ring system due to the patterning of aromatic rings.

3.4.4 Friedel-Crafts Cyclization

Given the landscape of our target molecules being rich in aromatic rings, employment of the Friedel-Crafts reaction stands out as the most likely candidate for successful ring formation. Drawing its origins to 1877,[27] this reaction has seen great utility in the context of total synthesis, with a select few examples of its use in nine membered ring formation as shown below. Representing a number of successful approaches to similar alkaloids, the total synthesis of quebrachamine (**39**) by Ziegler *et al.* is summarized in Scheme 7a with the key, ring forming step

Scheme 7. 9-Membered Ring Formation by Friedel-Crafts Reaction in a) Quebrachamine and b) Cyclotriveratrylene



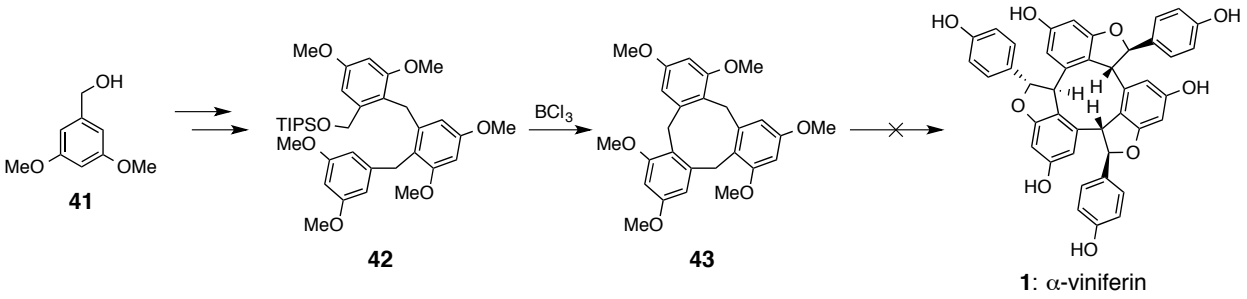
highlighted.[28] Here, treatment of carboxylic acid **37** with polyphosphoric acid effects acylation by the indole substructure to furnish **38**, likely through initial attack at the C-3 carbon followed by migration, a mechanism generally favored by the synthetic community.[29] Though this example involves the very specialized and well-documented reactivity of an indole heterocycle, in essence it showcases the power of a Friedel-Crafts cyclization to forge unfavorable rings, especially when accelerated by a conjugated electron-donating group such as the indole nitrogen. The abundant phenols of our system of interest would likely serve a similar role. The second example, though not in the context of natural product synthesis, is included due to its very clear relevance to our targets of interest with α-viniferin (**1**) being shown for comparison. In this reaction (Scheme 7b), the simple benzylic alcohol **40** was treated with acid, causing it to trimerize into nine membered ring **41**, cyclotriveratrylene, in an impressive yield of 71%.[30] Given the success of this, and related, Friedel-Crafts cyclizations to furnish ninemembered rings as well as the inapplicability of other established methods for their construction, we sought to apply Friedel-Crafts chemistry to access the key nine membered ring core of the applicable subclass of oligomeric resveratrol-based natural products as outlined in the following sections, hoping to develop new direction for its use in synthesis by designing novel applications and variations of its power.

3.5 Initial Efforts Towards the Synthesis of Nine Membered Ring Containing Resveratrol Oligomers

Given the rapid and relevant construction of a substituted cyclotriveratrylene (**41**, Scheme 7b) reminiscent of the resveratrol targets, we sought a similar approach towards our own molecules, one in which it was hoped that benzylic oxidation would allow for simultaneous

elaboration of all three methylene positions. As shown in Scheme 8, we were indeed able to synthesize the analogous nine membered ring **43** with an appropriate oxygenation pattern though a multistep sequence from key intermediate **42**; the single step procedure was ineffective with

Scheme 8. Attempted Elaboration to Natural Products Through Benzylic Oxidation



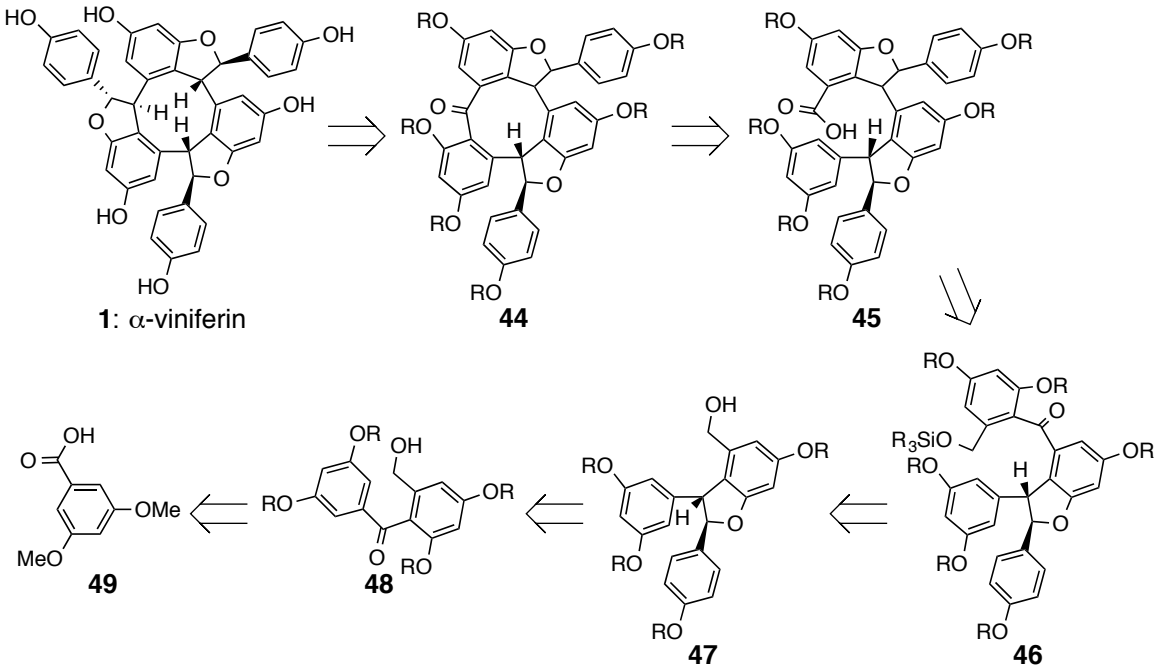
3,5-dimethoxybenzyl alcohol (**41**). Unfortunately, our initial efforts to elaborate that new product (**43**) were met with difficulty. Despite this setback, the intermediates and findings achieved during the course of these early studies have found application elsewhere. Such will be the focus of Chapter 4 with no further discussion taking place at this stage apart from noting that we deemed this approach unlikely to succeed for the formation of fully functionalized molecules of type **1** and proceeded to explore other Friedel-Crafts-based strategies.

3.5.1 Retrosynthetic Approach

Owing to the early difficulty experienced in preliminary benzylic oxidation attempts as noted in the previous section, we sought to install functional handles at the benzylic positions, if not the fully elaborated dihydrobenzofurans themselves, prior to nine membered ring formation. While the high degree of sp^2 hybridization in such a substrate would likely alleviate a great deal of the transannular interaction among substituents that often precludes medium-sized ring formation,[16] the rotational degrees of freedom available to the substrates would be significantly reduced as compared to their aliphatic counterparts. Whether this conformational restriction

would be to our benefit, or detriment, was unknown at the outset of our explorations. As shown in Scheme 9, we sought to elaborate to many, if not all, members of this resveratrol oligomer subclass from the common precursor ketone **44**; this material, with partially undefined stereochemistry, is itself a protected natural product: hopeachinol B (**10**, Figure 1). It was thought that the synthetic options from such a ketone starting point (and one found in Nature) would be sufficiently vast and varied so as to have a high chance of success in late stage divergence. In turn, we proposed to forge **44** though a Friedel-Crafts acylation of some carboxylic acid derivative such as **45**. While an acyl chloride seems the most straightforward and classically proven precursor for Friedel-Crafts chemistry,[31] should it fail to close the desired

Scheme 9. Retrosynthetic Approach To 9-Membered Ring Containing Resveratrol Oligomers



carbocycle, we hoped that with a highly electron-rich aromatic ring as nucleophile, some electrophilic component could be derived from the carboxylic acid for eventual success. Simplifying the structure further, we proposed **46** as a retrosynthetic precursor installing the dihydrobenzofuran within **45** through a strategy already established in our group.[32] Ketone **46**

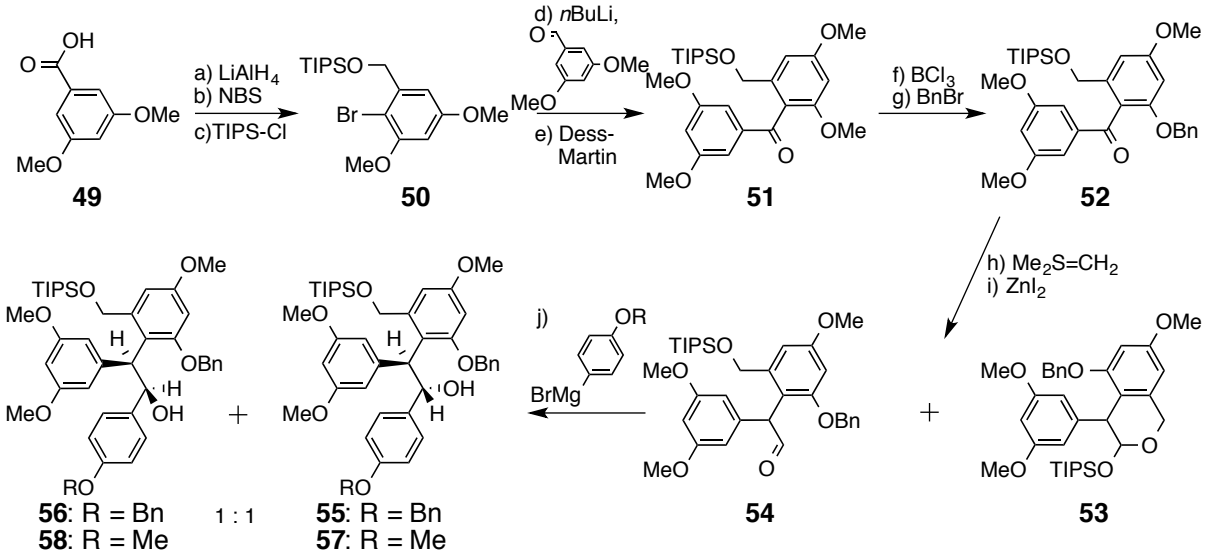
could, in turn, come from triaryl alcohol **47** which, in a process very similar to the above described steps, would result from elaboration of bisbenzylic ketone **48**; this new compound could be built from the inexpensive and commercially available 3,5-dimethoxybenzoic acid **49**. On first glance, it might seem curious that we have again chosen to begin with methyl ether protecting groups seeing as they required replacement in our syntheses of heimiol A and hopeahainol D (Chapter 2) and dihydrobenzofurans likewise have been shown to be sensitive to methyl ether cleavage conditions in multiple examples.[33] Despite these known limitations and the likelihood of an alternate protecting group scheme needing to be devised later, the methyl ether protecting groups were expected to provide a significant advantage during the "learning phase" of this project. Specifically, they give stability to the intermediates and, most importantly, clarity to the spectral data; benzyl ethers, the only other protecting group shown to be sufficiently robust to withstand the necessary transformations described, in contrast would hinder our ability to glean valuable information, particularly from ^{1}H and ^{13}C NMR data in our initial forays.

3.5.2 Synthesis of Triaryl Intermediate 60 and Selectivity in Dihydrobenzofuran Formation

In the forward direction, benzoic acid **49** first reduced to the corresponding alcohol and then regioselectively brominated using NBS; subsequent silylation then delivered **50** in excellent yield (Scheme 10). Lithium-halogen exchange and addition of the resultant nucleophile into 3,5-dimethoxybenzaldehyde then proceeded smoothly, with Dess-Martin oxidation[34] following to produce bis-benzylic ketone **51**. It is worthy to note that TBS protection of the alcohol proved unstable to the strong base treatment of *n*-BuLi, while TBDPS protection resulted instead in silyl

migration to the lithiated position; as such, the TIPS group was employed. Pressing forward, a single methyl ether was cleaved upon brief exposure to BCl_3, after which the phenol was reprotected as a benzyl ether to give **52**. While methyl protection of that position was critical for

Scheme 10. Synthesis of Dihydrobenzofuran Precursors.



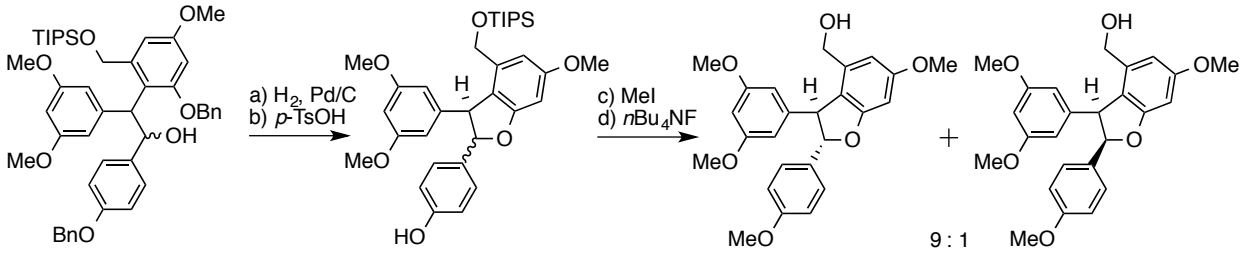
Reagents and Conditions: a) $LiAlH_4$, THF, 50 ºC, 1 h; b) NBS, CH_2Cl_2, 0 ºC, 12 h; c) TIPS-Cl, 1-Me-Imid., I_2 CH_2Cl_2, 25 ºC, 1 h, 93% from **49**; d) *n*-BuLi, THF, -78 ºC, 20 min, then add 3,5-dimethoxybenzaldehyde, 25 ºC, 12 h, 90%; e) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 25 ºC, 1 h 76%; f) BCl_3, CH_2Cl_2, 25 ºC, 10 min; g) BnBr, K_2CO_3, nBu_4NI, acetone, reflux, 12 h, 82% from **51**; h) Me_3SI, *n*-BuLi, THF, 0 ºC, 1 h; i) ZnI_2, benzene, 25 ºC, 15 min; j) 4-OBn-PhMgBr, THF, 25 ºC, 10 min, 95% from **52**.

the earlier coupling step, orthogonal protection was necessary during the subsequent dihydrobenzofuran forming step. The positional relationship of this single protected phenol with the neighboring ketone oxygen was critical to its selective removal as the ketone could coordinate the boron reagent and direct it towards the desired position, a phenomenon well documented in other instances.[35] At this point, the ketone was epoxidized using the Corey-Chaykovsky procedure[36] and that new function was isomerized to aldehyde **54** under the influence of ZnI_2,[37] a two-step sequence we found to be effective in other instances (see Scheme 8, Chapter 2). Unexpectedly, we recovered a second product from this reaction which we assigned as structure **53**. It appeared, based on close TLC monitoring of the reaction, that this side product was formed simultaneously with the desired aldehyde from the starting epoxide and

was, at least primarily, not formed subsequent to aldehyde formation. Although other Lewis acids were investigated to see if this product could be suppressed, the originally employed ZnI_2 was found to be the most successful in favoring aldehyde **54**. We later discovered that the side product **53** could be isomerized to a mixture with aldehyde **54** upon exposure to silica, although the amount of recovered aldehyde from this operation rarely warranted its use due to other unidentified products being formed as well and the separation proving rather tedious; in practice, the crude mixture of **53** and **54** was carried forward without purification as this was more easily achieved at a later step. Finally, Grignard addition onto this aldehyde delivered an approximately 1:1 diastereomeric mixture of benzylic alcohols **55** and **56**. With this sequence complete, we then set forth to forge the first dihydrobenzofuran system of the targets.

The reaction sequence begins with removal of the two benzyl ether protecting groups by hydrogenation (Scheme 11). This step must be monitored carefully as benzylic alcohol reduction has been observed upon extended exposure to the reaction conditions; unusually acidic palladium

Scheme 11. Synthesis of Dihydrobenzofuran Containing Substrates **60** and **61**.



55/56 : 1:1 mixture **59** **60** **61**

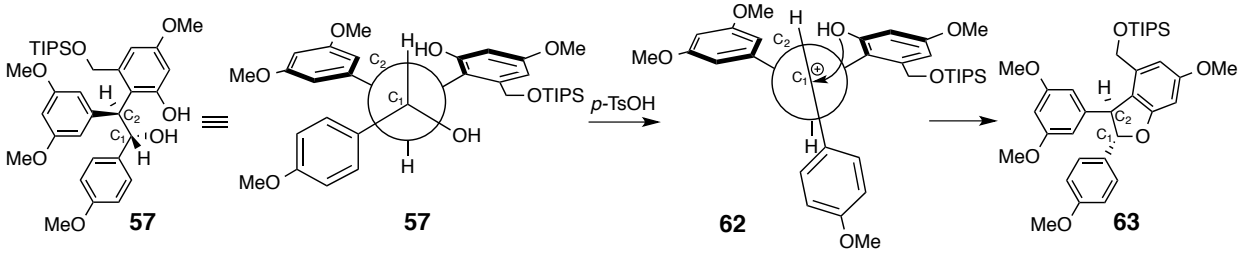
Reagents and Conditions: a) H_2, Pd/C, $NaHCO_3$, EtOAc/MeOH, 25 ºC, 4 h; b) *p*-TsOH, CH_2Cl_2, 25 ºC, 30 min; c) MeI, K_2CO_3, acetone, reflux, 4 h d) *n*Bu_4NF, THF, 25 ºC, 1 h, 92% yield from **55**/**56**.

catalysts will encourage this unwanted event and were buffered with solid $NaHCO_3$ as needed. Following vacuum filtration to remove the catalyst, the crude di-phenol was concentrated, re-dissolved in CH_2Cl_2, and exposed to *p*-TsOH to close the dihydrobenzofuran **59**, after which the remaining free phenol was protected as a methyl ether using MeI. Removal of the silyl

protecting group with nBu$_4$NF ultimately delivered a mixture of *trans*- and *cis*-disposed dihydrobenzofurans (**60** and **61**, respectively) favoring the *trans*- by approximately 9:1 on average, although ratios ranging from 7:1 to 15:1 were observed from different runs of this sequence; these compounds proved readily separable using standard flash chromatography. Upon initial inspection, it would appear that a better course of action to access **60**/**61** would be to bring in a methyl protected Grignard reagent since the benzyl ether is removed in the subsequent step and then replaced by a methyl group. In currently unpublished results by fellow group members Andreas Gollner and Maria Chiriac, these researchers had found that a protecting group on the *para*-substituted phenol during the dihydrobenzofuran cyclization gave poorer selectivity for the *trans*-product. Our own attempt on the *para*-methoxy versions of these compounds (**57** and **58**) confirmed that finding, as well as the fact the protection of the phenol resulted in longer reaction times. Wanting to more fully understand the reasoning behind these results, we separated the two diastereomers **57** and **58** and submitted them separately to *p*-TsOH in CH_2Cl_2 at 25 ºC. It was found that one diastereomer exclusively gave the *trans*-dihydrofuran containing product **60** at the end of the sequence while the other diastereomer gave a 1.6:1 mixture of **60** : **61**. Given that they presumably proceed through an identical cationic intermediate this outcome was curious. From these data we formed the following hypothesis outlined visually in Schemes 12 and 13 for the formation of the dihydrobenzofuran from each diastereomer.

In the Newman projection of **57**, we see the likely ideal rotamer about the indicated C_1-C_2 bond (Scheme 12). This conformation places the hydrogen atom of C_1 in between the two bulky aromatic rings of C_2 as well as the *para*-substituted aromatic ring of C_1 adjacent to the 3,5-dimethoxy aromatic ring of C_2 (as opposed to the more sterically encumbered 2,4,6-trisubstituted ring). Upon ionization of the hydroxyl group, we arrive at cation **62**, poised to form the more

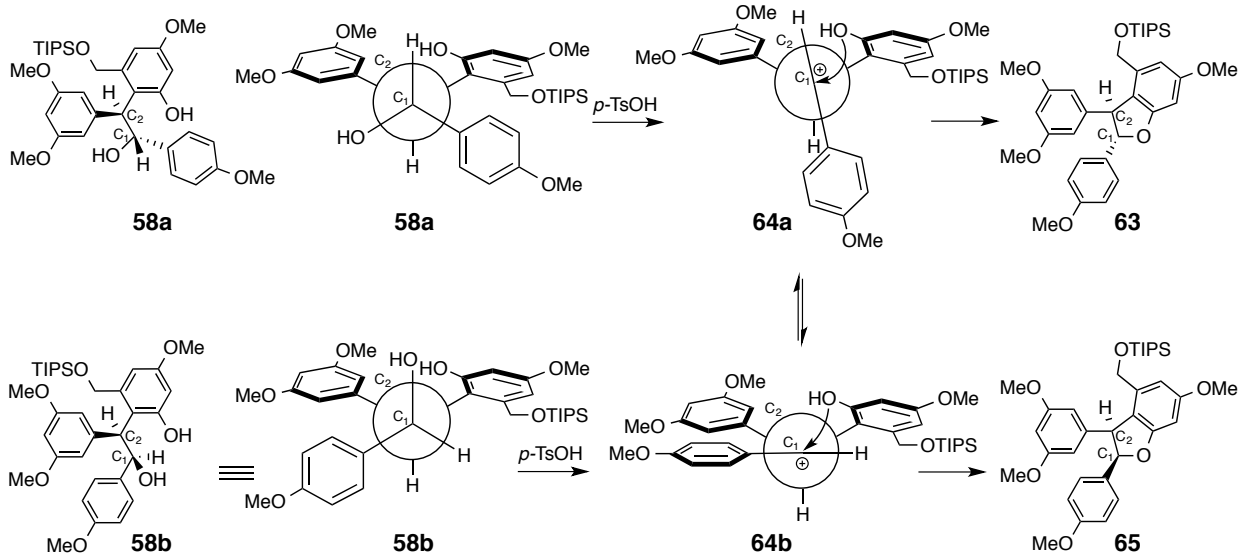
Scheme 12. Rationale For Dihydrobenzofuran Stereochemistry From Precursor **57**.



favored *trans*-dihydrofuran product (**63**) which would occur via the expected phenol attack. With an unlikely bond rotation to the less favorable rotamer being required for *cis*-dihydrobenzofuran formation, it would seem that **57** is the diastereomer which leads exclusively to a *trans*-dihydrofuran based on this analysis.

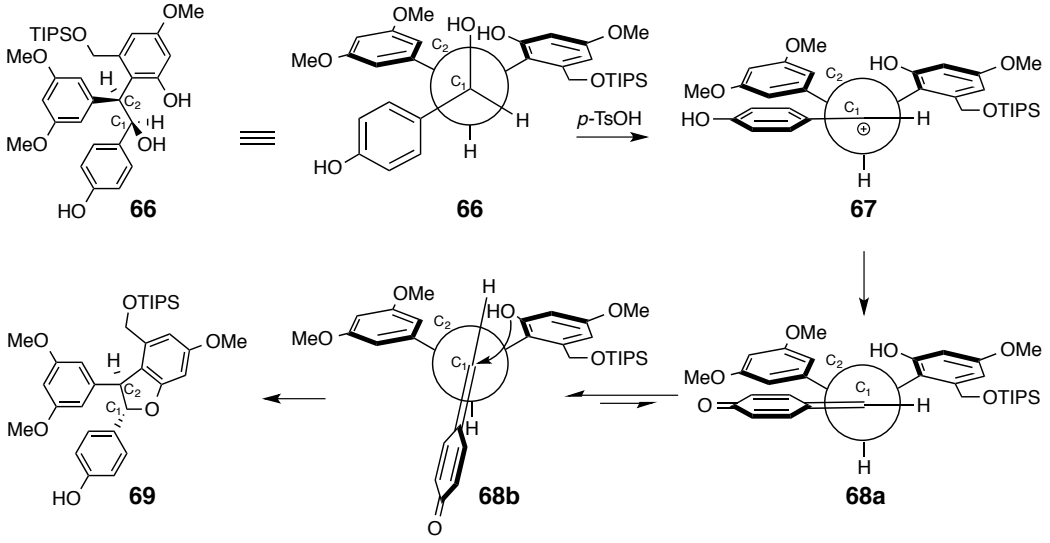
In the case of diastereomer **58**, the mechanistic process appears to be more complicated. As shown in the two Newman projections of **58**, the preferred rotamer about the indicated C-C is not as obvious. In the first Newman projection (**58a**) we favorably place the hydrogen atom of C_1 between the two sterically bulky aromatic rings of C_2. This positions the *para*-substituted ring of C_1, however, adjacent to the very bulky 2,4,6-trisubstituted aromatic ring of C_2, particularly with respect to its TIPS group. In the second Newman projection (**58b**), these two

Scheme 13. Rationale For Dihydrobenzofuran Stereochemistry From Precursor **58**.



rings are favorably *anti* to one another, although this then places the hydroxyl group of C_1 between the two aromatic ring of C_2 instead of the hydrogen atom. As shown, were the benzylic alcohol to occupy conformation **58a**, it would be poised to directly fashion the *trans*-disposed dihydrobenzofuran through the shown intermediate cation (i.e. **64a**) in much the same way as **57** (Scheme 12). If the conformation of the second Newman projection (**58b**) were favored prior to ionization, the cation conformation (compound **64b**) is seemingly predisposed towards the *cis*-dihydrobenzofuran product. While direct bond formation immediately following ionization would produce the *cis*-result, we see that rotation between **64b** and **64a** about the C_1/C_2 bond could then set up for closure to the *trans*-product which should be thermodynamically favored (Note: the favorability of the "pre-*trans*" cationic intermediate is also explained and supported by Snyder *et al*. in their synthesis of carasiphenol C).[32] Based on this analysis, we believe that **58** is the diastereomer leading to a mixture of the *trans*- and *cis*-dihydrobenzofuran-containing products (**63** and **65** respectively). This hypothesis is supported by the finding that a free phenol

Scheme 14. Cation Stabilization by Quinone Methide Formation Allowing For Isomerization To the More Stable *Trans*- Precursor **68b**.



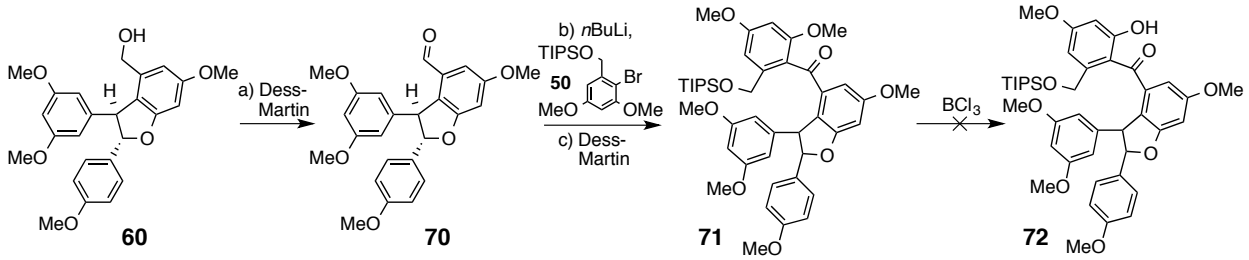
on the *para*-substituted ring enhances selectivity towards the *trans*-dihydrofuran. As shown in Scheme 14, the cation resulting from hydroxyl protonation and ionization is stabilized by the

para-disposed phenol. The stabilizing capacity of that phenol is increased if it is unprotected and thus able to make quinone methide **68** (Scheme 14). By stabilizing the cation, it is rendered slightly less reactive, allowing more time for rotation from **68a** to the more thermodynamically favored **68b** prior to phenol attack and ring closure. In the case of **64** where the phenol is protected, less stabilization is offered leaving the cation more "naked" and consequently more reactive which facilitates phenol attack and bond closure prior to rotation to the more stable rotamer (**63b**, Scheme 13). While transition state calculations were not performed in further support of this theory, we believe it provides a reasonable explanation for the observed outcome.

3.5.3 Elaboration To Nine Membered Ring Cyclization Precursors and Friedel-Crafts Acylation

With the first dihydrobenzofuran in place, elaboration to forge the second then proceeded as shown in Scheme 15. Dess-Martin oxidation of **60** efficiently gave the desired aldehyde **70**, after which aryl lithium addition and a second Dess-Martin oxidation furnished ketone **71** in good yield. Then, needing to remove the methyl ether adjacent to the ketone to later install a

Scheme 15. Failed Selective Methyl Ether Cleavage of **71**.



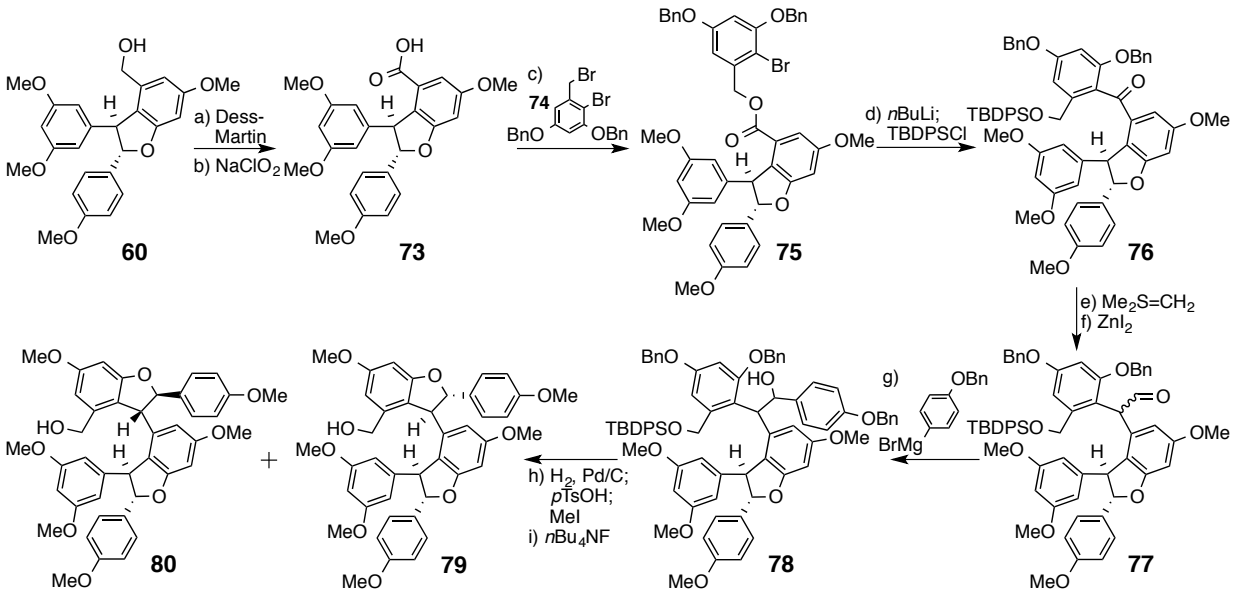
Reactions and Conditions: a) Dess-Martin Periodinane, $NaHCO_3$,CH_2Cl_2, 25 ºC, 1 h, 99%; b) *n*BuLi, **50**, THF, -78 ºC, 20 min, then **70**, 25 ºC, 4 h, 62%; c) Dess-Martin Periodinane, $NaHCO_3$, CH_2Cl_2, 25 ºC, 1 h, 99%.

dihydrobenzofuran analogous to the sequence in Scheme 14, we treated **71** with BCl_3. Unfortunately, this operation did not cleave the required methyl group to furnish **72**; prolonged exposure resulted in decomposition. Modeling using plastic kits revealed that the conformation

necessary for assistance by the neighboring ketone results in prohibitive steric interactions between other portions of the molecule. An alternate strategy was therefore devised for installing the fourth aryl ring of the target with orthogonal protection at the requisite phenol.

Thus, as shown in Scheme 16, Dess-Martin oxidation followed by Pinnick oxidation[38] effectively delivered carboxylic acid **73**. While many one step procedures have been developed for the direct conversion of a primary alcohol to the carboxylic acid, the majority of them required > two days before any noticeable amount of carboxylic acid product **73** was detected on this substrate. Jones reagent did deliver the carboxylic acid in a more timely fashion, however, the harshly acidic conditions appeared to decompose a portion of the material to give final,

Scheme 16. Installment of Second Dihydrobenzofuran Unit.



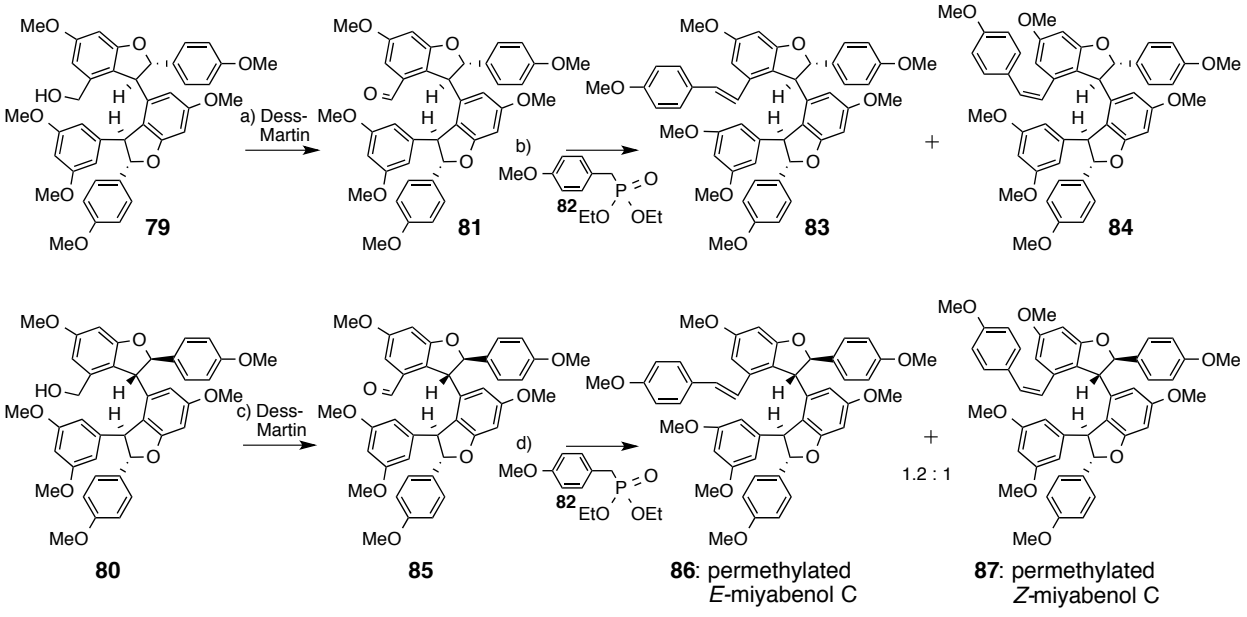
Reagents and Conditions: a) Dess-Martin Periodinane, $NaHCO_3$, CH_2Cl_2, 25 ºC, 30 min; b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/*t*BuOH/H_2O, 25 ºC, 12 h; c) **74**, K_2CO_3, *n*-Bu_4NI, acetone, reflux, 2 h, 85% from **60** d) *n*BuLi, THF, -94 ºC, 1.5 h, then TBDPS-Cl, DBU, 50 ºC, 12 h, 83% e) Me_3SI, *n*BuLi, 0 ºC, 1 h; f) ZnI_2, benzene, 25 ºC, 15 min; g) 4-OBn-PhMgBr, THF, 25 ºC, 10 min; h) H_2, Pd/C, EtOAc/MeOH, 25 ºC, 12 h, then *p*-TsOH, CH_2Cl_{225} ºC, 30 min, then MeI, K_2CO_3, acetone reflux, 12 h; i) *n*Bu_4NF, THF, 25 ºC, 1 h, 24% of **79**, 26% of **80** from **76.**

isolated yields of **73** in the range of 50-60%. On the contrary, the two step operation proceeded quickly, reliably, and in high yield. Subsequent alkylation of the carboxylic acid **73** with benzyl bromide **74** proceeded well. At this point, we treated ester **75** with *n*BuLi, achieving a lithium-halogen exchange with the lone bromide of that substrate to induce addition into the ester

carbonyl and subsequent expulsion of the benzylic alcohol in a homoanionic Fries rearrangement.[39] This new product, however, was found to be surprisingly unstable; indeed, the newly unveiled hydroxyl group required protection for much of the remaining steps and gratifyingly *in situ* protection as a silyl ether **76** proceeded smoothly. We found this overall sequence to be a very effective method for the synthesis of hindered bis-benzylic ketones, a strategy adapted from the Nicolaou group synthesis of balanol,[40] though our substrate **75** demonstrates the utility of this transformation in a far more complex setting. At this stage, a similar five-step sequence as employed previously for dihydrobenzofuran formation successfully accomplished the synthesis of diastereomeric intermediates **79** and **80**. The diastereomers were found to be easily separable by standard chromatography for subsequent elaboration to the target (and intermediates where their exact stereochemistry could be assigned).

Thus, wanting to determine the exact relative stereochemistry of each diastereoisomer, we embarked on the following sequence towards protected *E*- and *Z*-miyabenol C (Scheme 17).[41]

Scheme 17. Stereochemical ConfirmationVia the Synthesis of Permethylated *E*- and *Z*-Miyabenol C



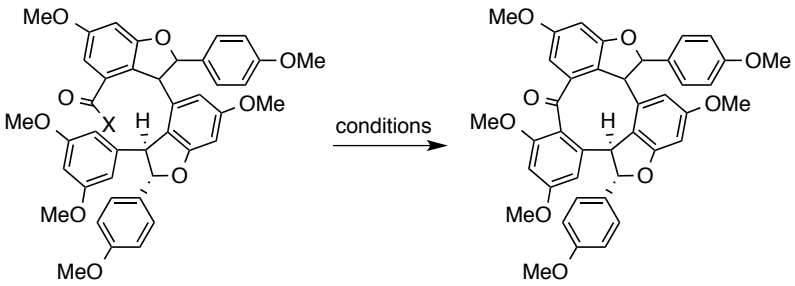
Reagents and Conditions: a) Dess-Martin periodinane, CH_2Cl_2, 25 ºC, 30 min, 99%; b) KO*t*Bu, **82**, THF, -78 ºC, 19 h 79%; c) Dess-Martin periodinane, CH_2Cl_2, 25 ºC, 30 min, 99%; d) KO*t*Bu, **82**, THF, -78 ºC, 1.5 h, 89%.

We assumed, with confidence, that the newly formed dihydrobenzofurans of **79** and **80** were *trans*-disposed given the coupling constants of their associated protons as compared with other dihydrobenzofuran containing substrates in this sequence, not to mention the overwhelming preference for *trans*-selectivity in similar scenarios. This analysis then leaves only **79** and **80** as the possible stereochemical outcomes. Separate oxidation of each to the aldehyde followed by Horner-Wadsworth Emmons olefination[42] using phosphonate **82**, gave the four products shown (**83**-**84**, **86**-**87**). While permethylated *E*- and *Z*-miyabenol C are not known in the literature, the similarity of NMR chemical shifts between the products of olefination from one of the two diastereomeric aldehydes **81** and **85** very closely resembled that of the natural products, while the other two were significantly different. Based on these data we tentatively assigned the relative stereochemistry of the two diastereomers and acted under this assumption for the remainder of the project. We recognize that this is not proof of the stereochemistry, but, an X-ray crystal structure of a later compound (Section 3.7) supports this assumption. In the end, the cyclization of either or both compounds would be useful and, as part of this exercise, we were able to synthesize permethylated variants of natural products *E*- and *Z*-miyabenol C (**86** and **87**).

At this stage we were well poised to begin exploring nine membered ring closing techniques. Oxidation of the two aldehydes **81** and **85** gave the corresponding carboxylic acids without trouble. Scheme 18, with its accompanying table, provides the results of our attempts to initiate an intramolecular Friedel-Crafts acylation, noting that each procedure was separately attempted with both diastereomers of the starting material. Formation of the acyl chlorides proceeded smoothly using $SOCl_2$ in CH_2Cl_2; unfortunately exposure to various Lewis Acids returned only hydrolyzed, starting carboxylic acids. Attempts to generate the acyl cation by sequestering the chloride with silver salts also failed to afford cyclized materials. Exposure to

BCl_3 ultimately led to decomposition, likely through acid-mediated dihydrobenzofuran opening. Formation of the methyl ester (compound **90**) went without incident, but exposure of it to strong

Scheme 18. Attempted Friedel-Crafts Acylations



Compound	X	Conditions	Result
88	Cl	$ZnCl_2$, DCM, 25 ^oC, 1 h	No Reaction
88	Cl	ZnI_2, DCM, 25 ^oC,12 h	No Reaction
88	Cl	BF_3•OEt_2, CH_2Cl_2, 25 ^oC, 1 h	No Cyclization
88	Cl	$AlCl_3$, CH_2Cl_2, 25 ^oC, 12 h	No Reaction
88	Cl	AgOTf, CH_2Cl_2, 25 ^oC, 1 h	No Reaction
88	Cl	AgO_2CCF_3 CH_2Cl_2, 25 ^oC, 1 h	No Reaction
89	OH	BCl_3, CH_2Cl_2, -78 ^oC, 20 min	Decomposition
90	OMe	BBr_3, CH_2Cl_2, -78 ^oC, 1 h	Decomposition
91	OTs	Tol. 100 ^oC, 12 h	No Cyclization
81/**85**	H	$SOCl_2$, DMF, 25 ^oC, 12 h	No Reaction
92	NMe_2	$POCl_3$, CH_2Cl_2, 25 ^oC, 12 h	No Reaction

boron-based Lewis acids merely led to its decomposition. In an interesting result, tosylation of the acid followed by simple heating produced three distinct compounds. While still unidentified, they all clearly possessed the three protons of the 3,5-dimethoxy substituted ring, indicating that the desired cyclization did not proceed. Aldehydes **81**/**85** were even treated with $SOCl_2$ in hopes of generating a geminal dichloride,[43] material which could cyclize leaving a single chloride for further manipulation, but this also gave no conversion. Finally, the dimethyl amide (**92**) was forged from the acid using dimethylamine and 1,1-carbonyldiimidazole in an effort to perform an intramolecular variant of the Vilsmeier-Haack reaction.[44] Unfortunately, in this case, only the clean starting amide was recovered after each attempt.

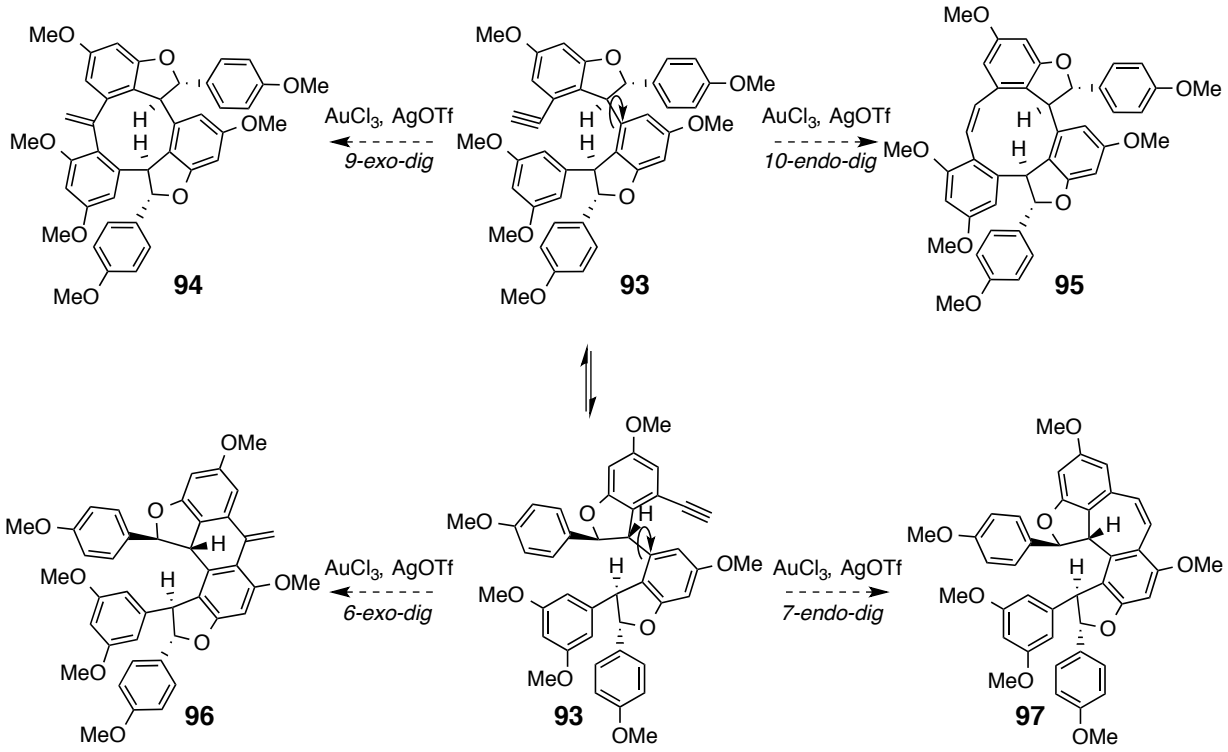
These results seemed to indicate that the electrophilic species was not forming due to a sterically encumbered environment around the carbonyl, though the ease of forming carboxylic acid derivatives appears to refute that hypothesis. Another theory would be that conformational restrictions in the molecule may have prevented the threshold proximity for productive bond formation from being achieved. As mentioned at the beginning of Section 3.5.1, the high number of rings and sp^2 hybridized atoms in our substrate significantly lowers the degree of rotational freedom available, a principle that would later prove itself both true and beneficial (*vide infra*). Nonetheless, at this point, we continued to explore Friedel-Crafts based approaches in order to exhaust the possible variations of this strategy before adopting a wholly different approach. Specifically, we next attempted gold-catalyzed cyclizations of alkynes and in so doing gained very illuminating insight into the conformational tendencies and nuances for substrates of this type in order to achieve a Friedel-Crafts-type cyclization.

3.5.4 Initial Studies Towards Gold Catalyzed Activation of Alkynes Towards Friedel-Crafts Based Cyclization

In the last decade there has been a veritable explosion of methodology development in the area of gold-catalyzed activation of alkynes and allenes towards nucleophilic attack.[45] Having been proven as a powerful method for effecting C-C bond formation, we sought to employ such reagents in the synthesis of our nine membered ring. Formation of alkyne **93** from preceding aldehyde **81** (not shown) was accomplished in 99% yield using the Ohira-Bestmann reagent,[46] at which point we began to explore cyclization conditions. Given that following activation of the alkyne there are two electrophilic carbons, a preliminary analysis of the potential reaction pathways was performed prior to engaging in actual laboratory experiments.

As shown in Scheme 19, there are four possible cyclization products that might be observed,

Scheme 19. Possible Cyclization Pathways For Gold Catalysis of Alkyne **93**.

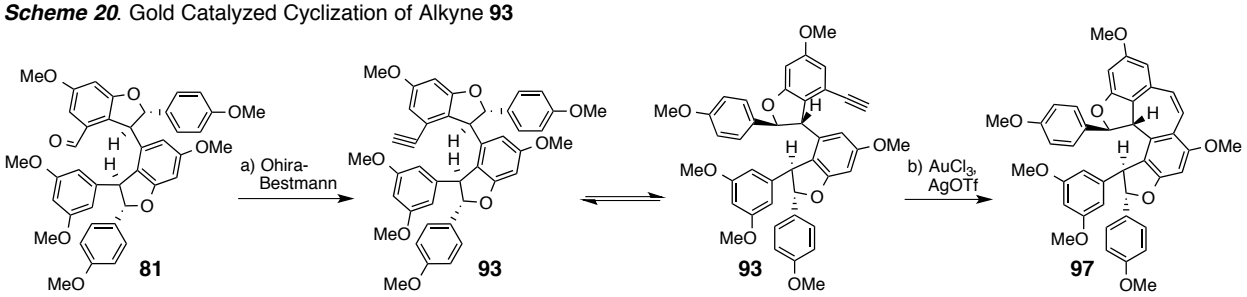


assuming successful alkyne activation and attack by an aromatic ring. The desired pathway represents a *9-exo-dig* cyclization leading to **94**. The same nucleophile/electrophile pair can also bond in a *10-endo-dig* manner to generate ten membered ring structure **95**. Such product mixtures of both *exo* and *endo* attack onto an alkyne are known in the literature and can often be manipulated based on the conditions or catalysts employed. Neither a *9-exo-dig* nor a *10-endo-dig* have ever been reported in any context..[47] Much more troubling in terms of alternatives to the desired outcome are made clear by the indicated bond rotation. In this conformation it is evident that *6-exo-dig* and *7-endo-dig* cyclization pathways are viable and give generally more favorable ring sizes (products **96** and **97**, respectively). Since Baldwin's rules often provide guidance as to the plausibility of certain ring forming reactions, we consulted them with reference to these four possibilities.[48] Unfortunately they offered little assistance as both the six

and seven membered ring forming cyclizations are allowed, and the nine and ten are not mentioned (with no prior examples to draw on as previously noted). In surveying these four possible outcomes, we sought insight through the use of plastic models, hoping to obtain a better understanding of the conformational tendencies of this particular system. In so doing, the *10-endo-dig* pathway was readily dismissed as an unlikely outcome. While the existence of such a ring did seem conceivable, there was a great deal of strain in the product and, more importantly, in the apparent transition state required to make the ring such that this outcome appeared highly improbable. While the unfavorability of a ten membered ring cyclization came as no surprise, the significant strain associated with the *6-exo-dig* pathway as indicated by the model was entirely unexpected. The fused, tricyclic 6,6,5 ring system, with one of the six membered rings being aromatic, appeared to incur a great deal of ring strain with the necessary bonding carbons being prohibitively far away in the alkyne starting material (**93**). This analysis indicating a low probability of six membered ring formation was supported by a number of failed experiments attempting to forge that ring intentionally; these will be detailed as part of a separate discussion in Section 3.9. Regarding both the *7-endo-dig* and the desired *9-exo-dig* cyclizations, the model suggested both to be reasonable outcomes. Neither pathway showed any obvious deterrents nor was a preference for one versus the other apparent.

In practice, as rendered in Scheme 20, the result of the reaction was a very clean and good conversion to seven membered ring **97**.[49] This outcome was supported by the presence of a *cis*- disubstituted alkene and the replacement of a pair of coupled protons in the ^{1}H NMR spectra with splitting consistent with a *meta* relationship by a singlet. The dihydrobenzofuran units remained intact. While this result was not the hoped for nine membered ring, nor was there even

Scheme 20. Gold Catalyzed Cyclization of Alkyne **93**



Reagents and Conditions: a) Ohira-Bestmann Reagent, K_2CO_3, MeOH, 25 ºC, 12 h, 99%; b) $AuCl_3$ (10 mol%), AgOTf (30 mol%), DCE, 25 ºC, 2 h, >90%.

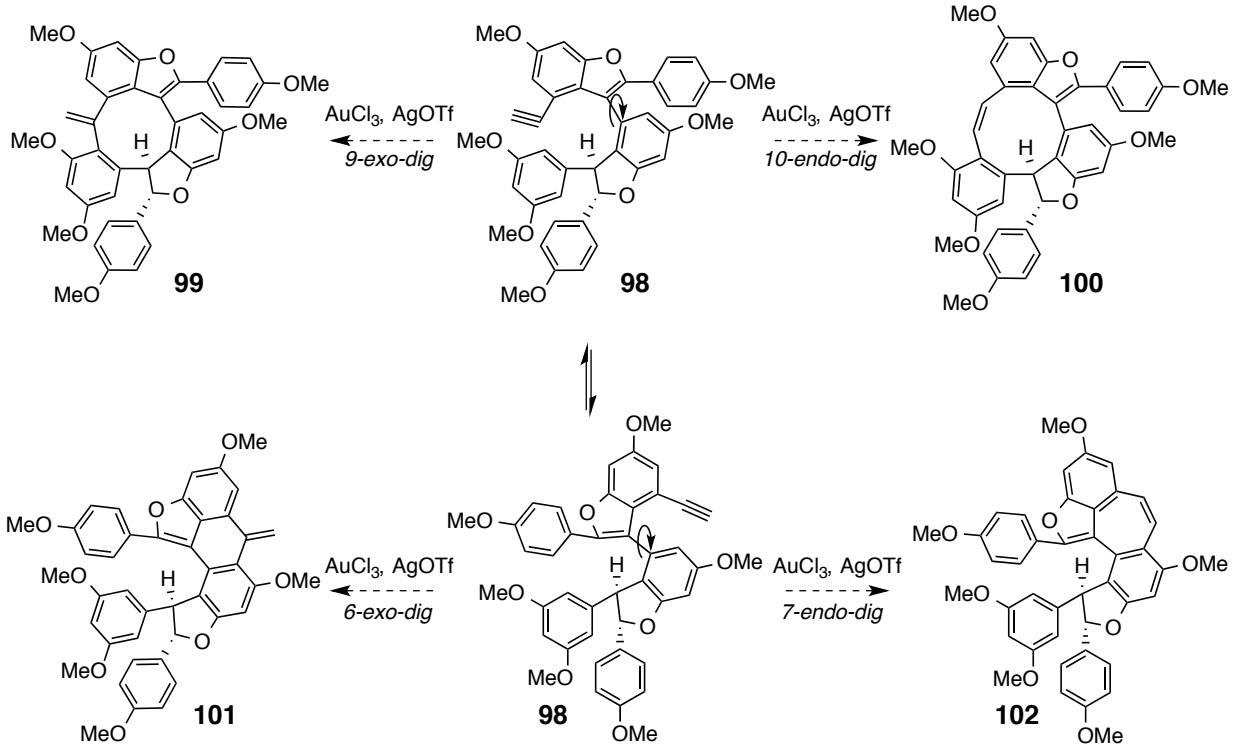
a trace of our desired product in the crude isolate, it proved the validity of this approach to a certain degree. The alkyne was effectively activated for nucleophilic attack by an aromatic ring, only it was the wrong aromatic ring that did the attacking. The task now was to devise a solution to this issue of selectivity by favoring attack by our desired nucleophile over its alternative. In a very basic and general sense, this outcome could potentially be accomplished either by making the desired pathway better or the undesired pathway worse.

3.5.5 Successful Nine Membered Ring Formation by Gold Catalysis

In an effort to uncover what modifications might bias this system towards the unobserved *9-exo-dig* pathway described above, we returned to plastic models. During the course of this exercise, no obvious/direct method for making nine membered ring formation more favorable came to light, however, a potential alteration to disfavor the observed seven membered ring cyclization was uncovered through a change in oxidation state. By converting one of the dihydrobenzofuran units into a fully oxidized benzofuran (substrate **98**), the strain associated with the *7-exo-dig* cyclization appeared to increase significantly. With all of the sp^2 hybridization in the ring, that lone sp^3 center of the seven membered ring of **97** (Scheme 19) significantly relieved the rigidity accompanying the alkene and two fused aromatic rings. Now, without that "kink" in the structure, product **102** in Scheme 21 appears less favorable. While the ground state energy of the products is a matter of thermodynamics and, given the irreversibility

of the addition, this reaction is generally assumed to be kinetically driven,[45] the likelihood of a

Scheme 21. Possible Cyclization Pathways For Gold Catalysis of Alkyne **98**.

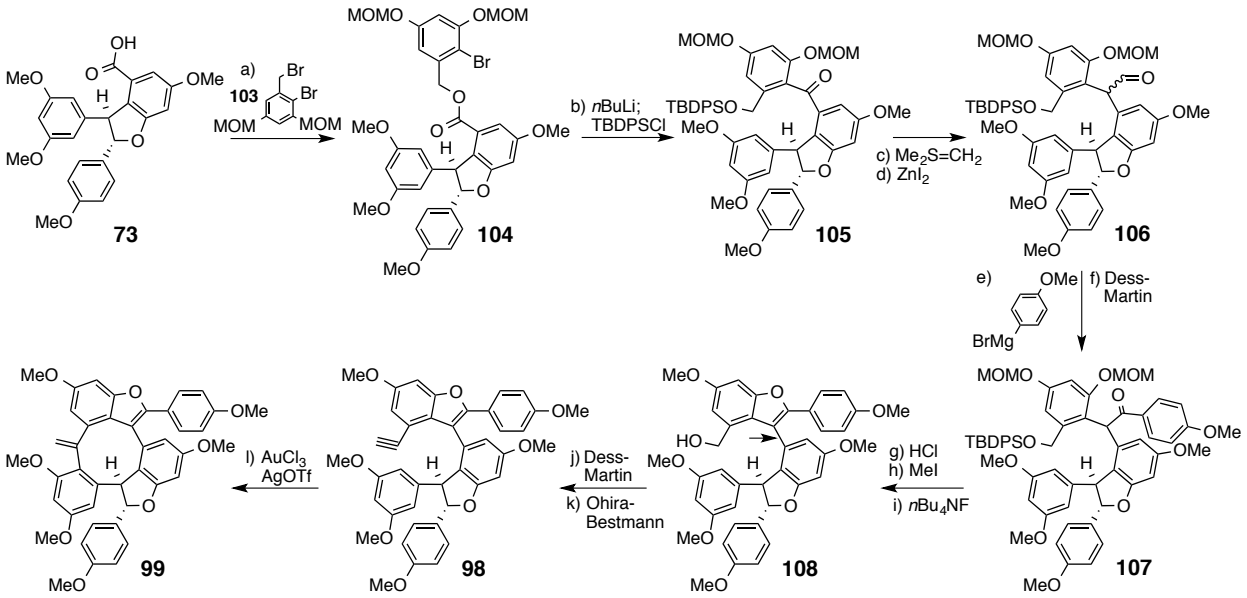


product-like transition state allows us to invoke the Hammond postulate towards making meaningful predictions regarding the reaction based on the ground state energy of the products compounds.[50] As such, upon reinvestigation of the four potential pathways now with a benzofuran in place (Scheme 21) we determined that the *10-endo-dig* and *6-exo-dig* pathways were still apparently improbable, ruling out **100** and **101**, and now, with higher strain incurred through the *7-endo-dig* pathway as well indicating that **102** is less likely to form, our confidence was high that we would observe nine membered ring formation, at least to some degree.

The synthesis of the benzofuran containing substrate is shown in Scheme 22. Beginning, as before, from carboxylic acid **73** (see Scheme 16), an alternate benzyl bromide was used to alkylate ultimately giving ester **104**. The process from this intermediate to aldehyde **106** is identical to that described previously with comparable yields achieved. The four diastereomeric

alcohols obtained after Grignard addition to aldehyde **106** (using *para*-methoxy Grignard as opposed to benzyloxy as employed previously) were then coalesced into two distinct ketones via Dess-Martin oxidation as shown in the form of structure **107**. At this point, treatment with HCl

Scheme 22. Synthesis of Cyclization Precursor **98** and Formation of 9-Membered Ring **99**.



Reagents and Conditions: a) **103**, K_2CO_3, *n*-Bu_4NI, acetone, reflux, 2 h, 96%; b) *n*-BuLi, THF, -94 ºC, 1.5 h, then TBDPSCl, DBU, 50 ºC, 12 h, 80%; c) Me_3SI, *n*BuLi, THF, 0 ºC, 1 h; d) ZnI_2, benzene, 25 ºC, 15 min; e) 4-OMe-PhMgBr, THF, 25 ºC, 10 min, 82% from **105**; f) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 25 ºC, 30min, 98%; g) HCl, THF/H_2O, 40 ºC, 4 h; h) MeI, K_2CO_3, acetone, reflux, 2 h; i) *n*Bu_4NF, THF, 50 ºC, 12 h, 53% from **107**, 2:1 atropisomer mixture; j) Dess-Martin periodinane, CH_2Cl_2, 25 ºC, 30 min, 99%; k) Ohira-Bestmann reagent, K_2CO_3, MeOH, 25 ºC, 12 h, 99%, 2:1 atropisomer mixture; l) $AuCl_3$ (10 mol%), AgOTf (30 mol%), DCE, 25 ºC, 2 h, >90% based on productive atropisomer.

accomplished the removal of both methoxymethyl (MOM) protecting groups and catalyzed cyclodehydration of the resulting substrate to form the actual benzofuran system. Methyl protection of the remaining free phenol and *n*Bu_4NF-enabled removal of the silyl protecting group gave alcohol **108**. Having dealt with diastereomers side-by-side in the previous approach (Scheme 16), we were excited to now have a single compound in our hands; however, upon isolating intermediates **108** and **109** we found that, in fact, two isomers were present. This observation was perplexing given that the only remaining stereocenters were those established many steps earlier and carried forward as the *trans*-dihydrobenzofuran. One explanation is that this ring had opened and partially isomerized to the *cis*-dihydrobenzofuran perhaps during HCl treatment. This hypothesis seemed, at least to us, unlikely for two reasons: 1) independent

experiments (not shown) had indicated that once formed, the opening, isomerization, and reclosing of these dihydrobenzofuran units is not a facile process with no successful approach for it found after many attempts and 2) the *cis*-dihydrobenzofuran is less favored, so if the ring did open, the probability of it isomerizing to the higher energy isomer is low and instead would likely reclose to the *trans*-variant. Our plastic models, however, indicated that there was the potential for atropisomers about the indicated bond (see arrow on **108**) and subsequently, this issue was found to be the case with these substrates, the details and implications of which will be discussed shortly.

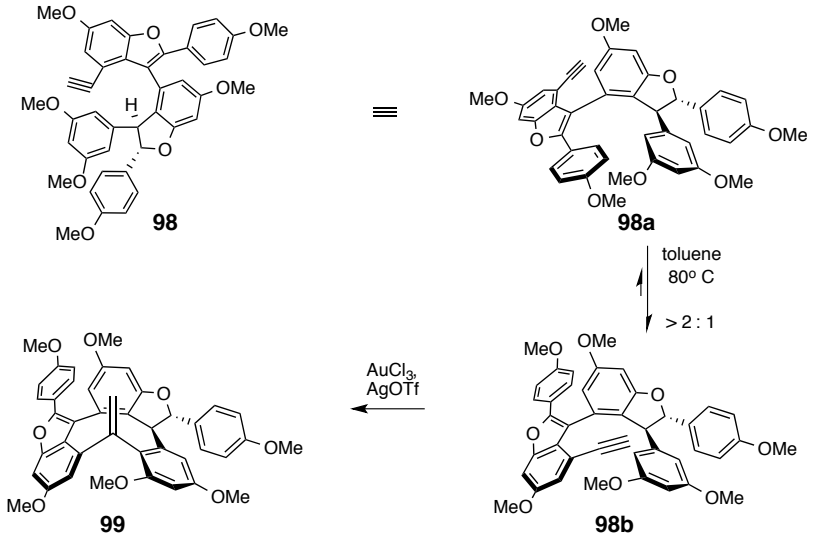
Nonetheless, pleased to have the benzofuran we pressed forward with the atropisomeric mixture of alkyne **109**, submitting it to the gold/silver reaction conditions as before (Note: other conditions of gold catalysis reported for similar transformations were attempted without success, see references for representative procedures).[47, 51] This event produced the desired nine membered **110** with great selectivity. After many months of building substrates and attempting cyclizations, we finally had a functionalized nine membered ring in hand. Interestingly, only one atropisomer reacted in this process as indicated (the yield shown is based on this atropisomer alone) while the other was recovered unchanged. In our efforts to understand this outcome, we gained valuable insight as to why this reaction was successful when so many others hade failed to forge the desired nine membered ring.

3.5.6 Atropisomers and Elaboration of the Nine Membered Ring 99

Shown in Scheme 23 is an attempt to provide a more accurate, three-dimensional rendering of the two atropisomers **98a** and **98b** as elucidated by plastic models of the substrate. We note that while plastic models certainly have their limitations, the general lack of

conformational freedom allows confident predictions based on the limited number of rotational options. As shown, the right-hand portion of molecule **98** forms a semi-bowl with a concave and convex face. In **98a**, the *para*-substituted ring of the left hand portion of the molecule occupies

Scheme 23. Atropisomers of Alkyne **98**.

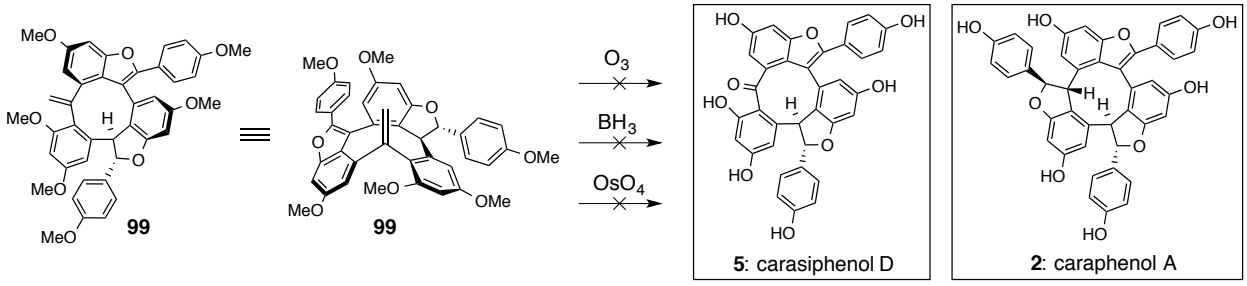


the concave face which forcibly places the alkyne moiety very far from its intended reactive partner, the 3,5-dimethoxy substituted aromatic ring of the right hand portion. We believe this to be the unreactive atropisomer. On the contrary, in isomer **98b**, the alkyne occupies the cavity and thus is held in direct proximity to the nucleophilic aromatic ring. It is this forced proximity in **98b** that allows, and possibly even encourages, the desired *9-exo-dig* cyclization to take place. Regarding the stability and interconversion of the two atopisomers, they are separable as the benzylic alcohols **108** (Scheme 22) and at all intermediates they do not interconvert at 25 ^{o}C allowing their separation and handling at ambient temperature without fear of unwanted isomerization. Submitting either atropisomer of **98** to heating in toluene at 80 ^{o}C for 24 h results in a >2:1 mixture favoring the productive atropisomer.[52] While **98a** and **98b** cannot be separated through conventional chromatography, the product mixture of the gold cyclization containing **98a** and **99** can be separated, with **98a** isomerized to a mixture of the two atropisomeric alkynes

later and the mixture resubmitted to the original reaction conditions to achieve throughput. This cycle may be repeated until virtually all material is brought through the productive pathway. Unfortunately, heating of the reaction mixture itself, in hopes of effecting an *in situ* isomerization and progression of all material, was unsuccessful and resulted in complete decomposition. Lastly, we note that this reaction is the first reported example of a *9-exo-dig* cyclization in any form in the literature.

With nine membered ring **99** in hand, we next sought to elaborate it to the natural products of interest. Having adopted the benzofuran, our directly available number of targets diminished, but we hoped that it could be reduced and manipulated at a later stage to reach the whole collection. For now, we targeted caraphenol A (**2**) and carasiphenol D (**5**), highlighted in Scheme 24. All that remained at this stage was to fashion the final dihydrobenzofuran from the

Scheme 24. Failed Attempts to Elaborate 9-Membered Ring Alkene **99**.

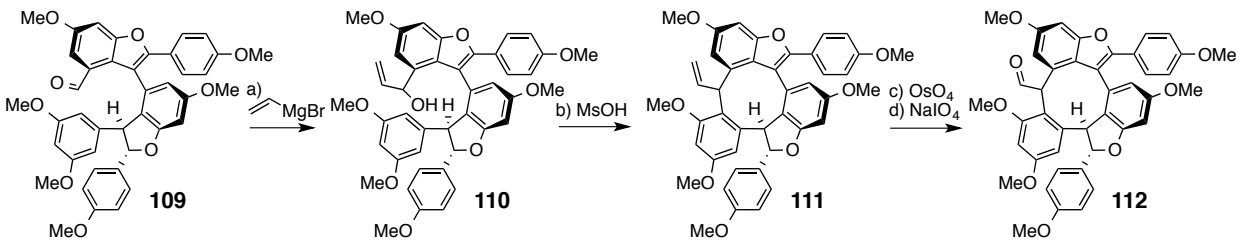


exocyclic alkene of **99** or to oxidatively cleave it to generate a protected form of **5**. As shown above, our joy at having obtained this substrate was short-lived as we quickly became acquainted with its recalcitrance towards standard reaction conditions. Ozonolysis decomposed the molecule entirely; this outcome was not completely surprising given the highly electron rich rings as well as the fact that benzofurans are known to cleave under these conditions.[53] Hydroboration gave no reaction under standard protocols. Finally, and most surprising, was the recovery of starting material after exposure to several equivalents OsO_4 at 50 ^{o}C over the course of four days with quinuclidine included as a ligand[54] to facilitate the process. The three

dimensional drawing of **99** perhaps gives a clue as to why such a lack of reactivity was observed. On the back face of the alkene lies a parallel aromatic ring, completely blocking any approach from that side. On the front face, although perhaps not entirely obvious from this drawing, lies a methoxy group that could prevent approach from that side as well. It seems that in generating the nine membered carbocycle in the previous step, the alkene is surrounded by other components of the molecule, rendering it inaccessible by incoming reagents. Additionally, with the olefin being entirely out of conjugation with the neighboring aromatic rings, the donating capacity of those rings is eliminated. As such they become only inductively withdrawing, a feature that likely also contributes to the unreactive nature of this olefin. Thus, not only do we need a successful nine membered ring forming reaction with functional handles for further manipulation, those functional handles must be sufficiently removed from the central steric congestion so that it can be accessed by necessary reagents.

According to this line of thought, we devised allylic alcohol **110** as shown in Scheme 25 as a new key substrate, easily obtained from the preceding aldehyde **109** by the addition of a vinyl Grignard reagent. If this substrate could cyclize to a nine membered ring, we would be left with a pendant vinyl group as opposed to the exocyclic alkene with the hope that this material would be less encumbered by steric congestion so as to allow for subsequent reaction. With the allylic alcohol, however, came a new set of possible reactive pathways (not shown) that could

Scheme 25. 9-Membered Ring Cyclization of Allylic Alcohol **110** and Subsequent Oxidative Cleavage



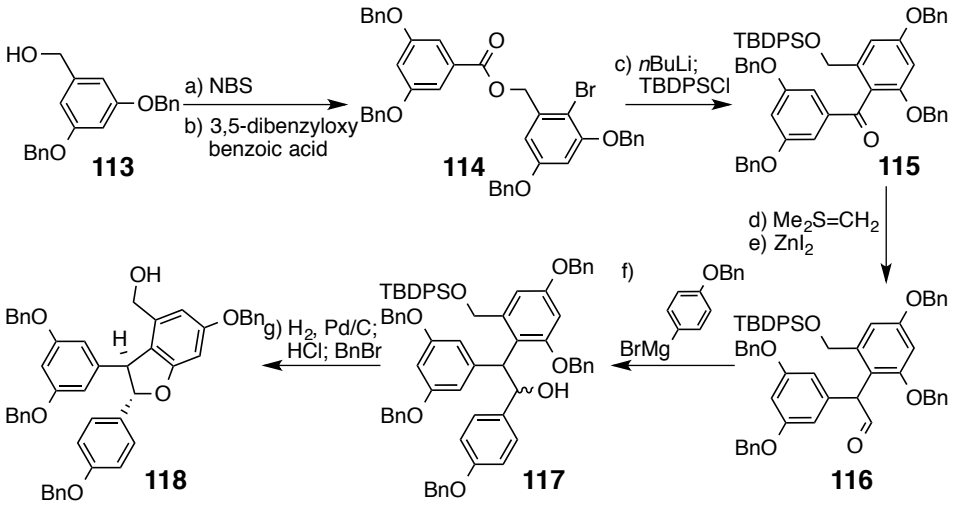
Reagents and Conditions: a) vinyl-MgBr, THF, 25 ºC, 10 min, 75%; b) MsOH, THF, 25 ºC, 3 h, 80%; c) OsO_4, NMO, acetone/H_2O, 25 ºC, 12 h; d) $NaIO_4$/ SiO_2, CH_2Cl_2, 25 ºC, 20 min, 75% from **111**.

lead to a number of ring sizes. Given the newly acquired knowledge regarding the nature of the atropisomers and the apparent propensity of one of them towards nine membered ring formation, we attempted the reaction. As shown, the desired cyclization was accomplished, delivering **111** in 80% yield. Brönsted acids produced the desired result with methanesulfonic acid (MsOH) being the most successful, while Lewis acids diverted the material towards alternative, non-productive pathways. We note here that, as with the gold cyclization of alkyne **98** (Scheme 22), only one atropisomer of the allylic alcohol (**110**) proceeded to cyclize to the nine membered ring while the other gave an entirely different result to be addressed more fully in Section 3.7. Nevertheless, with a second successful nine membered ring forming procedure in hand, it was now left to determine the accessibility of that olefin and, gratifyingly, it was found to give the desired aldehyde **112** under standard oxidative cleavage conditions. All that remained now was installment of the sixth and final aryl ring followed by closure of the dihydrobenzofuran. The phenol that would necessarily participate in that final dihydrobenzofuran closure is, as are all of the other phenols, protected as a methyl ether with its deprotection proving overly harsh under standard conditions for these late stage intermediates. This outcome was known when embarking upon this route as mentioned in Section 3.5.1 with the reasoning that methyl ether protecting group provide an ideal setting to become familiar with polyphenolic systems of this type and develop synthetic solutions for their construction. Thus, with a successful synthetic strategy in place, we sought to now accomplish the full total synthesis of a nine membered ring containing resveratrol oligomer using a late-stage cleavable protecting group array.

3.6 Total Synthesis of Caraphenol A

While the majority of the route to be described in this section closely mirrors that of the permethylated structures outlined earlier in Section 3.5, several portions exhibited key differences which will be highlighted as they are described. Given prior experience exploring the suitability of various protecting groups on scaffolds of this general class of molecules, benzyl ethers were chosen as the most likely candidate to withstand the various reaction conditions employed in the developed sequence while still being cleavable under mild conditions at its conclusion. Beginning with commercially available 3,5-dibenzyloxy alcohol **113**, treatment with

Scheme 26. Synthesis of Triaryl Intermediate **118**.



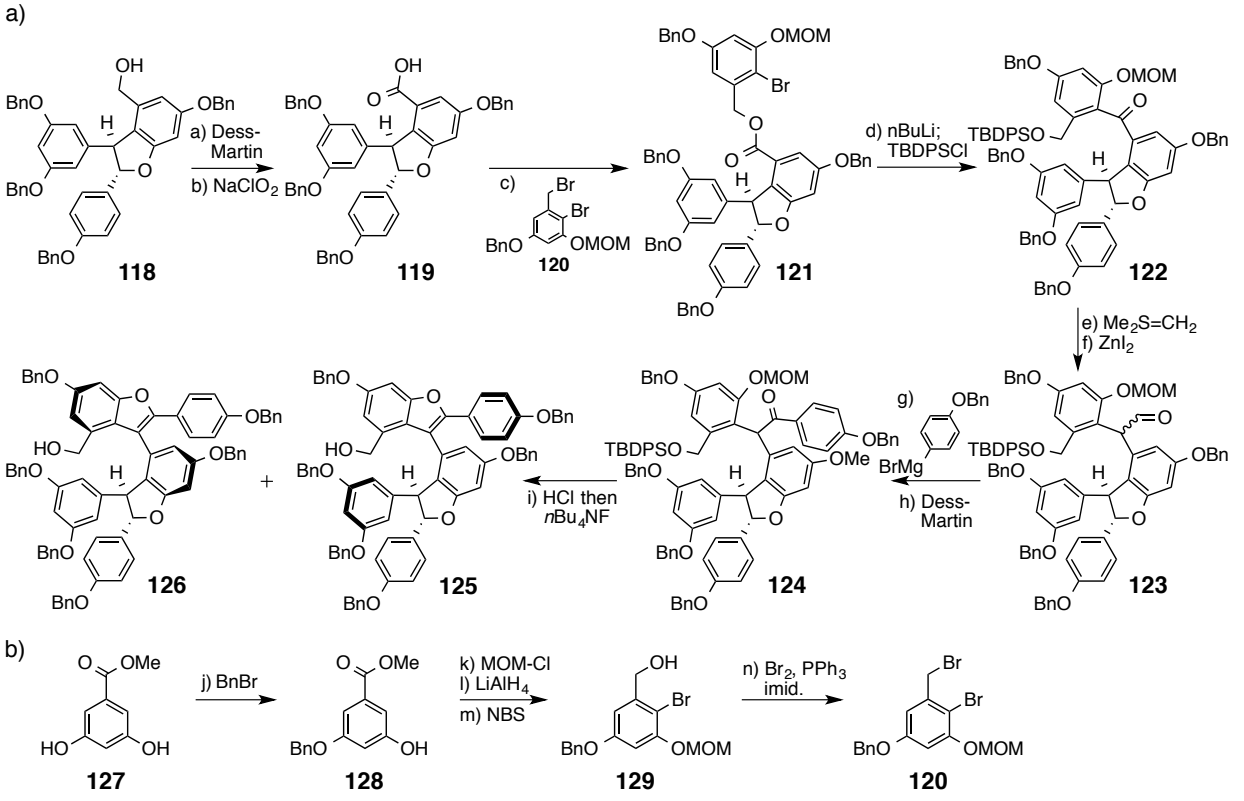
Reagents and Conditions: a) NBS, CH_2Cl_2, 0 ºC, 12 h, 99%; b) PPh_3, DIAD, 3,5-dibenzyloxybenzoic acid, THF, 0 ºC, 15 min, 91%; c) *n*BuLi, THF, -105 ºC, 1.5 h, then TBDPS-Cl, DBU, 50 ºC, 12 h 83%; d) Me_3SI, *n*BuLi, THF, 0 ºC; e) ZnI_2, benzene, 25 ºC, 15 min; f) 4-OBn-PhMgBr, THF, 25 ºC, 10 min, 74% from **115**; g) H_2, Pd/C, EtOAc/MeOH, 25 ºC, 6 h, then HCl, MeOH, 25 ºC, 6 h, then BnBr, K_2CO_3, nBu_4NI, 25 ºC, 12 h, 80%, 10:1 diastereomeric mixture favoring **118**.

NBS effected the desired regioselective bromination and was followed by a Mitsunobu reaction[55] with 3,5-dibenzyloxybenzoic acid to furnish ester **114**. After a rapid silica plug to remove the Mitsunobu byproducts, this material was purified by crystallization to afford pure **114** in > 90% yield over the two steps. At this stage, a previously discussed (Section 3.5.3), homoanionic Fries rearrangement with concomitant benzylic alcohol protection was effected by treatment with

*n*BuLi at low temperature followed by warming and the addition of TBDPS-Cl to give ketone **115**. The analogous transformation of alcohol **113** to ketone **115** with regard to the methyl ether protected variant (Section 3.5.2, Scheme 10, **49** to **52**) required six steps as opposed to the three shown here. This difference is due to the inability to implement effectively the Fries rearrangement to a permethylated precursor because of poor solubility of the methyl variant in the very low temperatures required for the rearrangement. Secondly, in the methyl protected case, a single methyl group needed to be removed and replaced by a benzyl to allow subsequent dihydrobenzofuran formation to take place whereas in the present case, this two step sequence is not needed. Carrying forward, the same three step protocol as employed previously on bisbenzylic ketones delivered alcohol **117** as a mixture of diastereomers. Global benzyl group removal was then accomplished via hydrogenation, after which the catalyst was removed, a solvent switch to pure MeOH performed, and dihydrofuran formation achieved by HCl treatment. Heating the acidic mixture was also found to remove the silyl protecting group thus obviating the need for a later protecting group removal by including that operation at this juncture. Removal of the HCl and MeOH by rotary evaporation was immediately followed by selective benzyl protection of the four free phenols leaving the benzylic alcohol untouched, delivering **118** in one pot from **117** as a 10:1 mixture of *trans*- and *cis*-dihydrobenzofurans favoring the *trans*-variant. Pleasingly, these diastereomers were easily separable by flash chromatography. While we must concede that the atom economy of this procedure is less than optimal with the removal of five benzyl groups only to replace four of them, other protecting group schemes proved ineffectiveor incompatible with the reaction conditions necessary to the sequence. The strategy described here being the most successful and reliable.

Pressing forward, oxidation to the carboxylic acid **119** (Scheme 27) proceeded without incident after which the ester (**121**) was formed by alkylation with benzyl bromide **120** (its synthesis is shown in Scheme 27b). Though **120** could be produced with improved regioselectivity using alternate strategies, the methods shown allowed for the most efficient material throughput and purification. Homoanionic Fries rearrangement was accomplished, as before, to give ketone **122**. The main side-product observed in each instance of this reaction is *n*BuLi addition to the ester carbonyl, a pathway that could be suppressed upon cooling, hence the low reaction temperatures reported in the conditions for these procedures. Elaboration from **122** to ketone **124** is accomplished effectively in an 82% yield over the four steps identical to those performed in the synthesis of **107** as described earlier in the context of Scheme 22.

Scheme 27. a) Synthesis of Atropisomers **125**/**126** b) Synthesis of Bromide **120**.

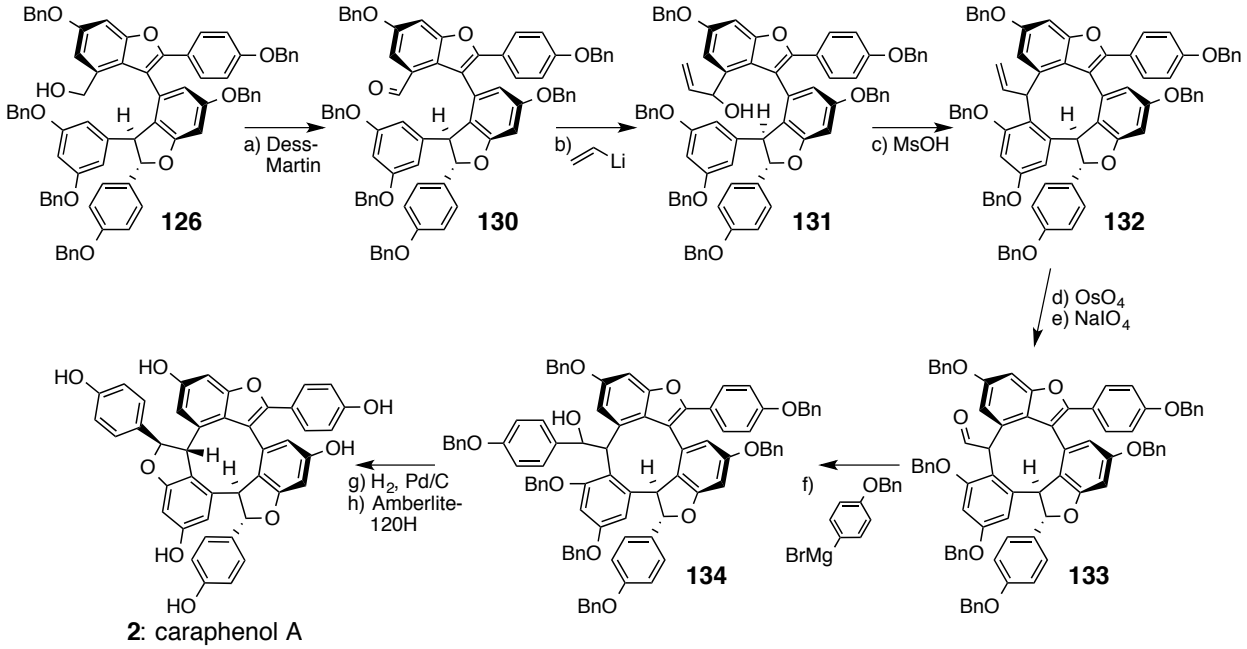


Reagents and Conditions: a) Dess-Martin Periodinane, $NaHCO_3$, CH_2Cl_2, 25 ºC, 30 min; b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/*t*BuOH/H_2O, 25 ºC, 12 h; c) **120**, K_2CO_3, *n*-Bu_4NI, acetone, reflux, 2 h, 85% from **118**; d) nBuLi, THF, -94 ºC, 1.5 h, then TBDPS-Cl, DBU, 50 ºC, 12 h, 80%; e) Me_3SI, nBuLi, THF, 0 ºC, 1 h; f) ZnI_2, benzene, 25 ºC, 25 min; g) 4-OBn-PhMgBr, THF, 25 ºC, 10 minl; h) Dess-Martin periodinane, CH_2Cl_2, 25 ºC, 30 min, 82% from **122**; i) HCl, THF/MeOH, 25 ºC, 12 h, then *n*Bu_4NF, 50 ºC, 12 h, 88%, 1:1mixture, converted to 2.8:1 mixture favoring **126** by tol. 80 ºC, 24 h; j) BnBr, K_2CO_3, *n*Bu_4NI, acetone, reflux, 12 h, 41% from **127**; k) MOM-Cl, DIPEA, CH_2Cl_2, 25 ºC, 30 min,87%; l) $LiAlH_4$, THF, 25 ºC, 5 min, 99%, m) NBS, CH_2Cl_2, 0 ºC, 12 h, 62% plus 34% regioisomer n) Br_2, PPh_3, imid., CH_2Cl_2, 0 ºC, 30 min, 99%.

Treatment with HCl effected MOM group cleavage and cyclodehydration to form the benzofuran unit, after which simple addition of nBu$_4$NF to the reaction mixture accomplished removal of the silyl protecting group to furnish **125**/**126** in a single pot from ketone **124**. Alcohols **125**/**126** were isolated as a mixture of atropisomers as previously observed with **98**, with warming in toluene favoring interconversion to the productive atropisomer **126** by a margin of 2.8:1. This mixture could be separated with the unproductive isomer re-equilibrated to a 2.8:1 mixture repeatedly, thus converting nearly all available material to a productive pathway in a few cycles.

Oxidation of **126** to the aldehyde (**130**), followed by vinyl lithium addition cleanly produced allylic alcohol **131** as shown in Scheme 28. Unexpectedly, use of a vinyl Grignard reagent gave up to 20% aldehyde reduction back to alcohol **126**. This process has been known to

Scheme 28. Completion of the Total Synthesis of Caraphenol A.

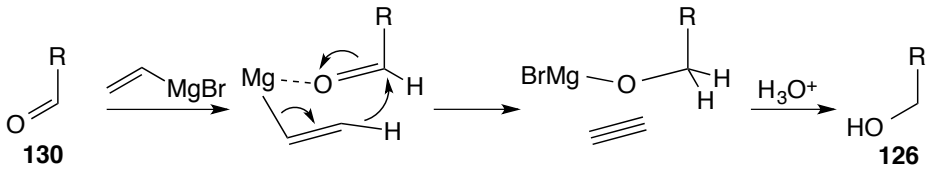


Reagents and Conditions: a) Dess-Martin periodinane, CH_2Cl_2, 25 ºC, 30 min, 93%; b) vinyl lithium, THF, -78 ºC, 5 min; c) MsOH, THF, 50 ºC, 45 min, 73% from **130**; d) OsO_4, NMO, acetone/H_2O, 8 h; e) $NaIO_4/SiO_2$, CH_2Cl_2, 25 ºC, 1 h, 76%; f) 4-OBn-C_6H_4-MgBr, THF, 25 ºC,10 min, 95%; g) H_2, Pd/C, EtOAc/MeOH, 25 ºC, 3 h; h) Amberlite-120H, MeOH, 25 ºC, 2 h, 83% from **134**.

occur with some alkyl Grignard reagents,[56] although to the best of our knowledge such an outcome with vinyl magnesium bromide is unknown. We believe this reaction occurs via

coordination of the aldehyde oxygen to magnesium followed by acetylene formation and hydride delivery through a six membered ring transition state as shown in Scheme 29. Due to the lacking

Scheme 29. Possible Mechanism For Aldehyde Reduction With Vinyl-MgBr



potential for any additional coordination, vinyl lithium adds to the aldehyde cleanly, although, it was observed that excess vinyl lithium addition led to unknown side products. This issue was fortuitously solved by the fluorescent color of aldehyde **130** which, due to a conjugated donor/acceptor complex between the *para*-substituted methoxy group and the aldehyde moiety through the benzofuran, is very bright green in color. Simple titration of this fluorescent color with a freshly prepared solution of vinyl lithium until it disappeared ensured no over addition. Much to our relief, nine membered ring formation to **132** and the subsequent oxidative cleavage to give aldehyde **133** was then accomplished with equal success as in the permethylated model system. In this case, the newly formed stereocenter was assigned based on an observation on the plastic model system wherein the antipode would force the atoms of the carbonyl, and its preceding olefin, directly into the aromatic ring across from it. Further discussion on this point is provided in Section 3.8.

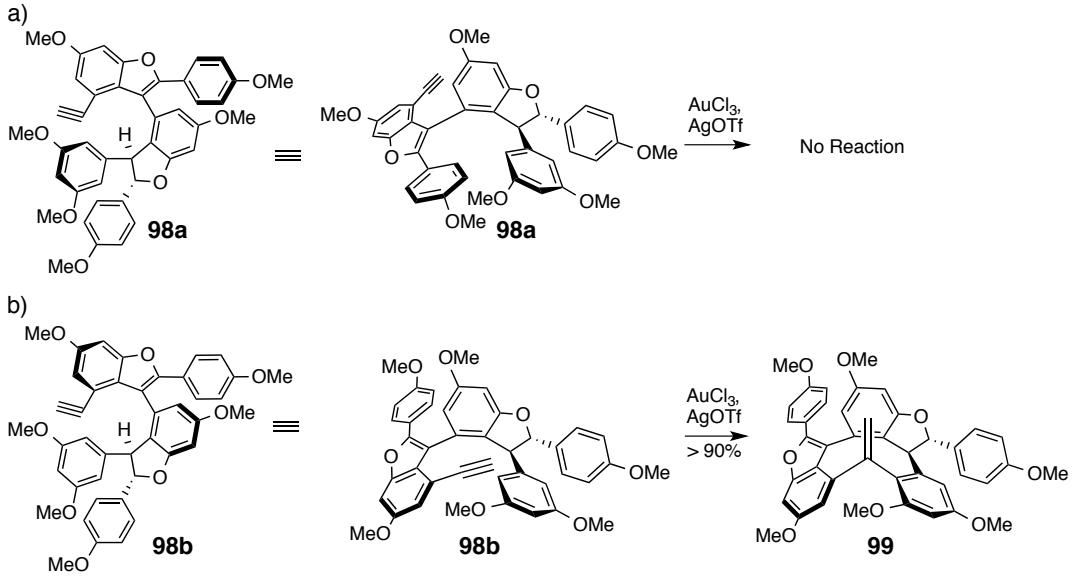
Pressing forward, addition of the last aryl ring as a Grignard reagent proceeded as expected, giving **134**, and finally, hydrogenation to remove all seven benzyl groups, followed by brief acid treatment, closed the final dihydrobenzofuran bond to give caraphenol A (**2**). This route was carried out in a total 23 steps from commercial material for the longest linear sequence and in an overall yield of 7.8% (89.5% average per step). In addition to the high yield of the sequence, each step was performed on at least a 1 gram scale to deliver hundreds of milligrams

of **2**. We believe this sequence represents a powerful example of effective and scalable total synthesis towards highly complex and challenging natural product frameworks.

3.7 Efforts Towards Other Nine Membered Ring Containing Resveratrol Oligomers

As previously mentioned, our goal in this endeavor did not end with the synthesis of a single natural product in this subclass. Rather, we hoped to synthesize all twelve natural products shown in Figure 1. In our efforts to do so, we found that not only was our solution to caraphenol A very successful, it was very unique. The following schemes give a sense of this with three-dimensional renderings provided as they are deemed helpful to the overall discussion. Some results from previous sections will be reiterated here as they provide a complete picture of the cyclization attempts as shown in systematic fashion beginning with Scheme 30. Shown are two nine membered ring cyclization attempts with each atropisomer of alkyne **98**. According to

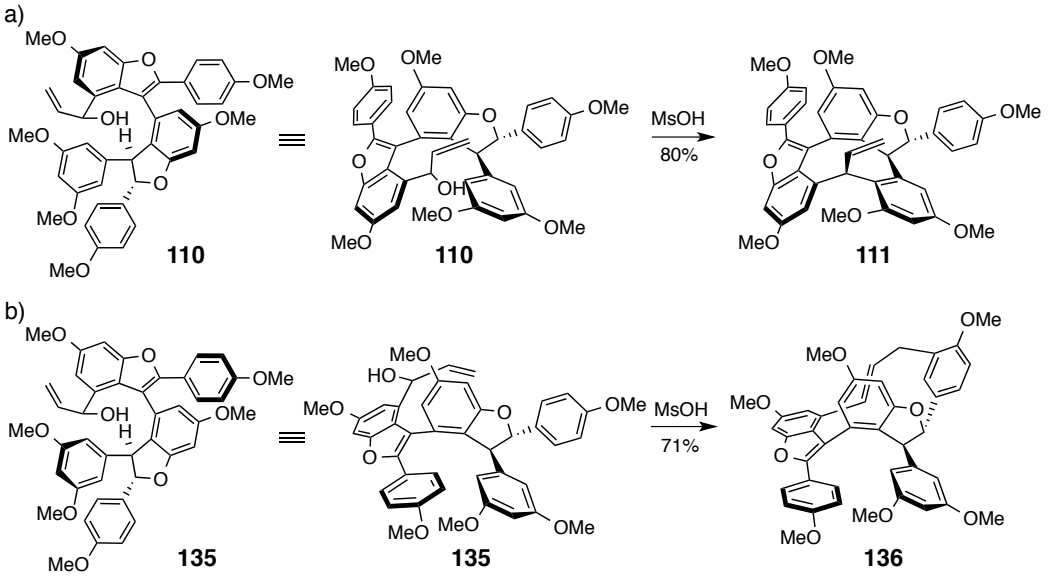
Scheme 30. Gold-Catalyzed Cyclizations of a) **98a** and b) **98b**.



the previously provided explanation, **98a** is unable to forge the desired bond and with no other viable reactive pathways available it is recovered unchanged. Conversely **98b** is poised for nine membered ring formation and does so smoothly. Scheme 31 shows the same two atropisomeric

frameworks, but as compounds **110** and **132** with an allylic alcohol as the electrophile. In this case, **110** possesses the same conformational benefit as **98b** in Scheme 30, and as such, proceeds to the desired carbocycle with a pendent vinyl group as described previously, this substrate being the one that was carried forth to the completion of caraphenol A. In Scheme 31b is shown a new result, specifically the isolated product upon cyclization of the other atropisomer, **135**. While the alkyne in the previous case represents a two carbon electrophile with the potential for reaction at either end, the allylic alcohol can be characterized as a three carbon electrophile with the potential for reaction at either end. This added carbon allows the indicated *para*-substituted ring opportunity to access the *in situ* generated allylic cation and forge a unique, and very unexpected, 13-membered ring (**136**) as drawn. Despite its complex structure, the conformation

Scheme 31. Acid Promoted Cyclization of Allylic Alcohols a) **110** and b) **135**.

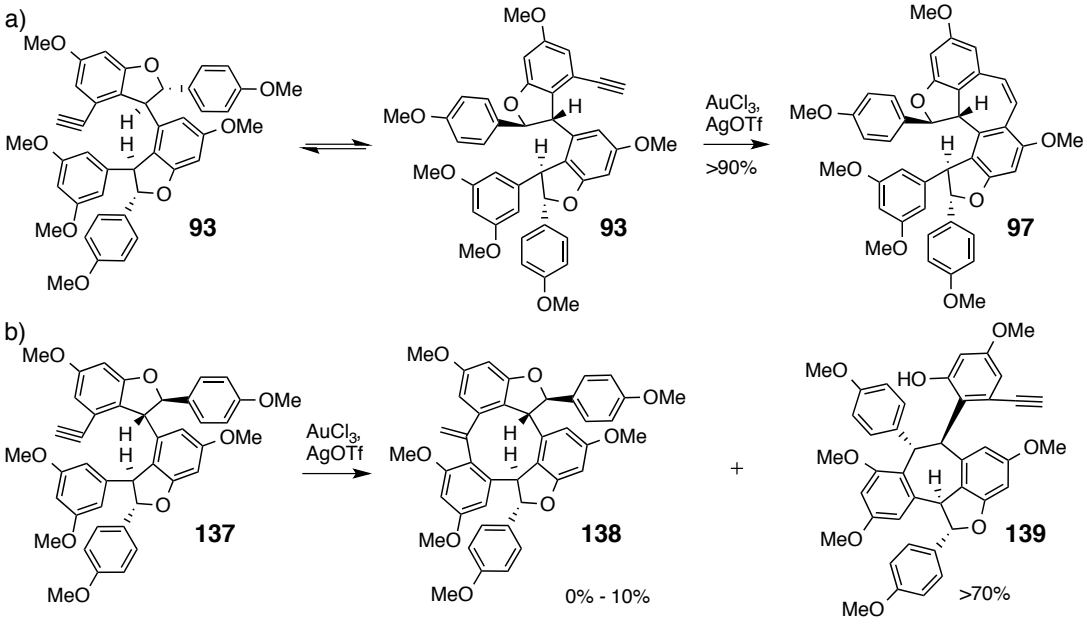


of **136** drawn appears to minimize significantly any strain associated with the 13-membered ring as well as any steric interaction among substituents. We note that the olefin geometry of **136** is unconfirmed. It is assigned here as *E*- based on that isomer being the less strained model as well as the coupling constants being more consistent with a *trans*-disubstituted double bond. We acknowledge, however, that both pieces of evidence are circumstantial and given the convoluted

nature of this compound, *Z*-geometry is entirely possible. Having surveyed both sets of successful conditions on each atropisomer of the benzofuran-containing substrates we then moved on to the all dihydrobenzofuran-containing cyclization precursors.

Shown in Scheme 32 are the gold-catalyzed cyclization results as performed on the two diastereomeric compounds **93** and **137**. Reiterated in part a) of that scheme is the *7-endo-dig* cyclization of **93**, the reaction which was our first attempt utilizing this method. Not mentioned previously was the same procedure carried out on the other diastereomer, compound **137**. In this case, a small amount of the desired nine membered ring **138** was formed during approximately half the attempts. The majority of isolated material, and the only isolated product during some

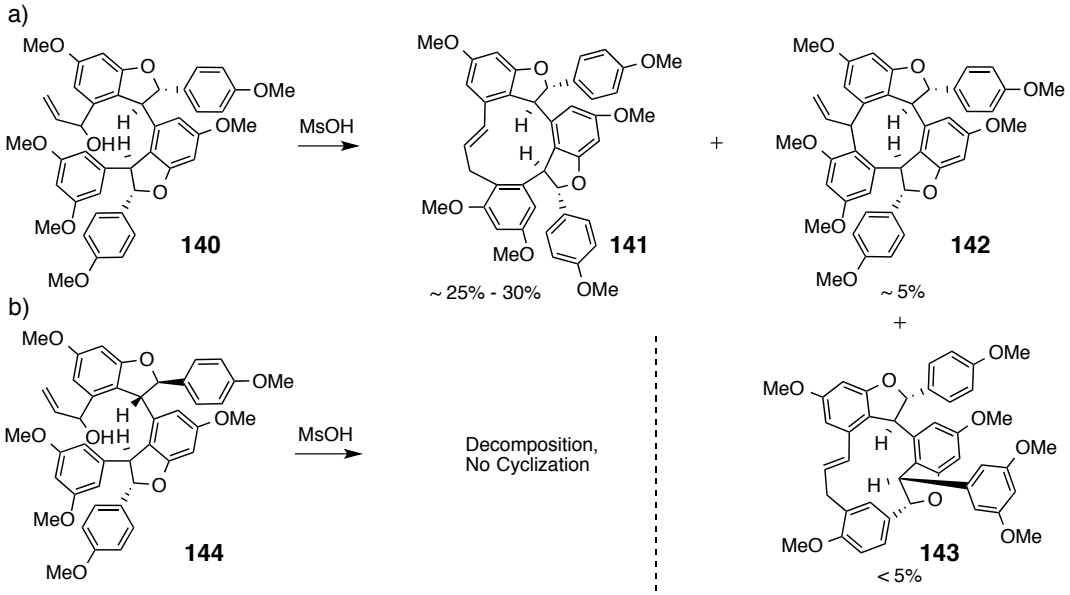
Scheme 32. Gold-Catalyzed Cyclizations of Alkynes a) **93** and b) **137**.



attempts, however, was the seven membered ring **139** with its unreacted alkyne. This product was entirely unexpected and results from opening of the dihydrobenzofuran and attack onto the newly generated benzylic cation by the 3,5-disubstituted aromatic ring. Whether this occurs in an S_N1 or an S_N2-like mechanism is unknown. At no point previously during the course of this project was a dihydrobenzofuran opened and the resulting cation attacked to give a non-

decomposed product. Ultimately, the structure and stereochemistry of **139** was determined by X-ray crystallographic analysis. Moving on to Scheme 33, the allylic alcohol cyclization was applied to both dihydrobenzofuran-containing compounds **140** and **144** with very mixed results obtained. Isomer **140** reacted to give four products that were isolated and characterized. The most abundant was eleven membered ring **141**, the possibility of which was acknowledged in each allylic alcohol cyclization attempt though this substrate was the only one to produce it. This new product (**141**) was initially believed to be the nine membered ring given the correct nucleophile and electrophile obviously being engaged. Subsequent oxidative cleavage of the double bond revealed two aldehydes correspondeding in all ways to being derived from the eleven membered ring. The olefin geometry is tentatively assigned as *E*- based on the same

Scheme 33. Acid Promoted Cyclization of Allylic Alcohols a) **140** and b) **144**.

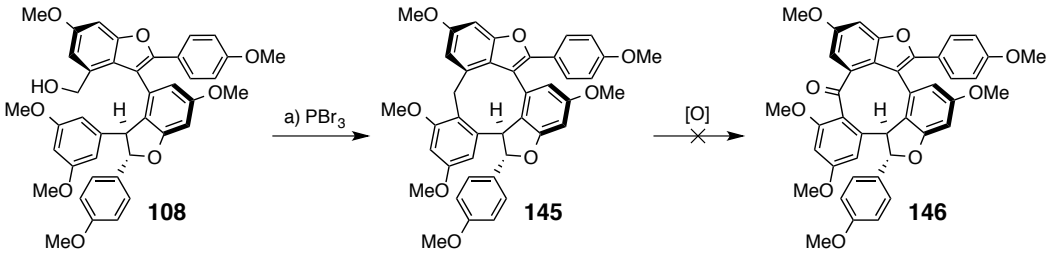


arguments as with 13-membered ring compound **136**. A small amount of desired nine membered ring **142** was also recovered as well as 13-membered ring **143**, forged in an identical fashion as **136** (Scheme 31b). These two products came as an inseparable mixture along with other unidentified products; however, upon dihydroxylation with OsO_4, their diol counterparts were

easily separated by preparative TLC after which $NaIO_4$ gave the aldehydes. The product aldehydes were characterized and the preceding alkenes deduced as a result. Finally, a significant amount of rearranged allylic alcohol was identified and found to be unreactive under the reaction conditions (not shown). Given the potential utility of nine membered ring **142**, various Bronsted and Lewis acids were attempted in different solvents and temperatures in hopes of enhancing selectivity for this product. Unfortunately, none successfully increased that selectivity for **142**. Despite this array of isolated and characterizeable products from the reaction of **140**, its diastereomer (**144**) produced no cyclization whatsoever with only decomposition observed and a small amount of potential allylic alcohol rearrangement. Taking Schemes 30-33 together, each possible iteration of the two successful nine membered ring forging conditions is shown on the relevant substrates with two of them reliably producing nine membered rings in a worthwhile yield (**99** and **111**) and only one of them delivering a compound capable of elaboration to a natural product.

One concluding cyclization in shown in Scheme 34. During one exploration we saw fit to transform benzylic alcohol **108** into the corresponding bromide. In so doing we recovered primarily the nine membered ring containing product **145**. Wanting to elaborate this material at

Scheme 34. Cyclization of Alcohol **108**.



Reagents and Conditions: a) PBr_3, pyr., Et_2O, 35 ºC, 1 h, 75%.

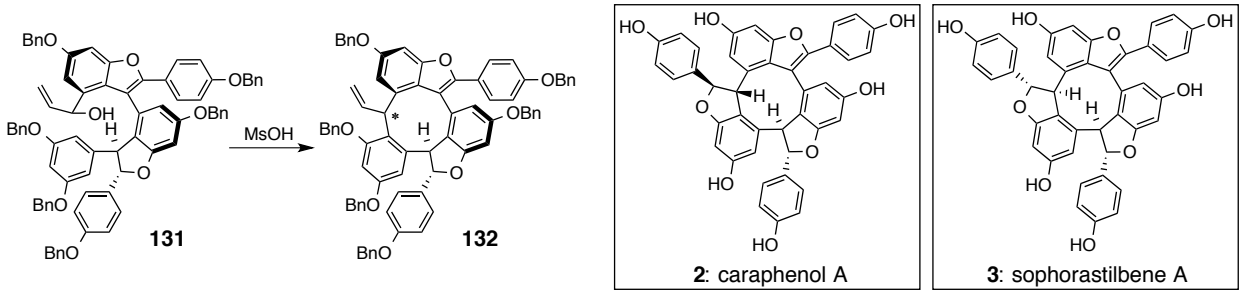
the newly formed methylene bridge we sought to oxidize **145** to protected carasphenol D (**146**), unfortunately to no avail. Though disappointed at the inability of these methods to furnish other

natural products in this subclass, a great deal of new and unforeseen pathways were uncovered during the course of this exercise lending a greater understanding to the conformational and reactive tendencies of these fascinating molecules.

3.8 Structural Assignments of Caraphenol A and Sophoarastilbene A

Upon forming a new chiral center in the conversion of allylic alcohol **131** to nine membered ring **132**, shown again in Scheme 35, we obtained a single product indicating its formation to be diastereoselective. As the configuration of this newly formed stereocenter would impact the ultimate final product, we sought to identify it. According to the published structures

Scheme 35. Stereochemistry About Newly Formed Stereocenter In **132**.



of caraphenol A[1b] and sophorastilbene A,[1c] either epimer of **132** would lead to a natural product and being so close to the end of the sequence we deemed completion of the synthesis to be the most straightforward and reliable way of assigning the stereocenter. This elaboration was done as described in Section 3.7, yet an interesting finding surfaced upon comparison of our final product to that of caraphenol A and sophorastilbene A: all three sets of NMR data were essentially identical (Tables 1 and 2 below). A uniform shift of δ -0.5 ppm was applied to the ^{13}C-NMR data and δ -0.02 ppm was applied to the ^{1}H-NMR data of sophorastilbene A, accounting for what is likely calibration difference. The only glaring discrepancy lies in a data point in the ^{13}C-NMR wherein the peak of sophorastilbene A is δ 5.4 ppm higher than its

counterpart in caraphenol A and our synthetic natural product. Suspicious of these data, a plastic model was fashioned of each reported structure to gain insight into their three dimensional conformation. Upon doing so it was found that the reported structure of caraphenol A adopts an unstrained molecular arrangement while the reported structure of sophorastilbene A has no conformation within reach that even remotely relieves the strain incurred upon building it. While

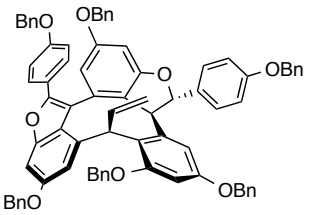
Table 1. ^{1}H NMR Data Comparison for Caraphenol A and Sophorastilbene A.

Caraphenol A	Sophorastilbene A*	Difference
7.26 (8.7 Hz)	7.26 (6.4 Hz)	0
7.24 (8.6 Hz)	7.26 (6.9 Hz)	0.02
7.05 (8.6 Hz)	7.05 (8.3 Hz)	0
6.94 (1.8 Hz)	6.93 (1.8 Hz)	-0.01
6.81 (1.8 Hz)	6.79 (1.8 Hz)	-0.02
6.80 (8.7 Hz)	6.79 (6.4 Hz)	-0.01
6.75 (8.6 Hz)	6.74 (6.9 Hz)	-0.01
6.71 (8.6 Hz)	6.70 (8.3 Hz)	-0.01
6.54 (1.8 Hz)	6.54 (1.8 Hz)	0
6.52 (2.1 Hz)	6.49 (1.8 Hz)	-0.03
6.32 (2.1 Hz)	6.32 (1.8 Hz)	0
6.25 (1.8 Hz)	6.25 (1.8 Hz)	0
5.92 (s)	5.91 (s)	-0.01
5.91 (s)	5.91 (s)	0
4.87 (s)	4.85 (s)	-0.02
4.31 (s)	4.34 (s)	0.03

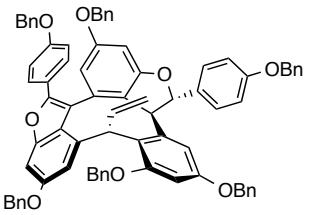
Note: A -0.02 ppm shift has been applied to Sophorastilbene A data.

ring strain and relatively high ground state energy are by no means grounds for dismissal of a structural assignment, this finding, in combination with the NMR data, impose serious doubt as to the claim that these are in fact separate compounds. Modeling alkenes **132a** and **132b** showed that **132b** would induce an extremely unfavorable steric interaction between the pendant vinyl

Figure 2. Possible Diastereomers of Alkene **132**.



132a: pre-caraphenol A



132b: pre-sophorastilbene A

Table 2. ^{13}C NMR Data Comparison for Caraphenol A and Sophorastilbene A.

Caraphenol A	Sophorastilbene A*	Difference
45.7	45.9	0.2
54.1	54.0	-0.1
87.9	87.9	0.0
95.2	95.1	-0.1
96.4	96.4	0.0
97.6	97.6	0.0
98.3	98.4	0.1
108.7	108.7	0.0
108.8	108.7	-0.1
109.7	109.7	0.0
114.5	114.5	0.0
115.9	115.8	-0.1
116.0	116.0	0.0
116.2	116.1	-0.1
118.9	119.1	0.2
120.6	120.7	0.1
122.7	122.9	0.2
127.4	127.4	0.0
122.8	128.2	5.4
128.2	128.3	0.1
128.3	128.3	0.0
132.5	132.7	0.2
133.5	133.6	0.1
135.3	135.3	0.0
139.7	139.7	0.0
141.0	141.0	0.0
149.3	149.6	0.3
155.2	155.2	0.0
157.2	157.0	-0.2
158.0	157.9	-0.1
158.2	158.0	-0.2
158.3	158.1	-0.2
159.2	159.1	-0.1
159.8	159.9	0.1
160.7	160.5	-0.2
163.5	163.5	0.0

Note: A -0.5 ppm shift has been applied to Sophorastilbene A data.

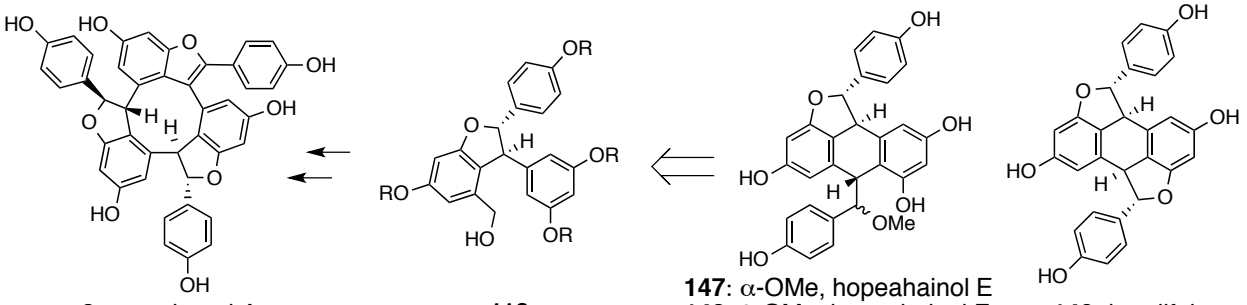
group and the aromatic ring directly across the central carbocycle as depicted in the three dimensional drawing (Figure 2). Additionally, were that to in fact be the product it would be essentially impossible for dihydrobenzofuran formation to occur since the benzylic carbon to be

attacked would be out ofreach for the requisite phenol. These observations are consistent with the conclusion that our synthetic final target corresponds to the reported structure of caraphenol A. Unfortunately, attempts to secure actual ^{1}H and ^{13}C NMR spectra from the isolation chemists were unsuccessful, preventing confirmation that the one outlying peak of the reported sophorastilbene ^{13}C NMR data are either typos or artifacts. While it is possible that these two structures in reality have strikingly similar NMR profiles, based on the data and observations presented here it is the opinion of this author that caraphenol A (**2**) and sophorastilbene A (**3**) are in fact the same compound and correspond to the reported structure of caraphenol A (**2**) whose spectra matches that obtained by our total synthesis.

3.9 Development of a New Common Intermediate and Its Application to Other Members of the Resveratrol Family of Oligomers

In developing the synthetic route to caraphenol A (**2**), the triaryl, dihydrobenzofuran containing intermediate **118** was produced (Scheme 36), shown here with a generic protecting group scheme. Upon surveying the numerous resveratrol-based oligomeric natural products, it

Scheme 36. Potential Role of **118** As a Common Intermediate.

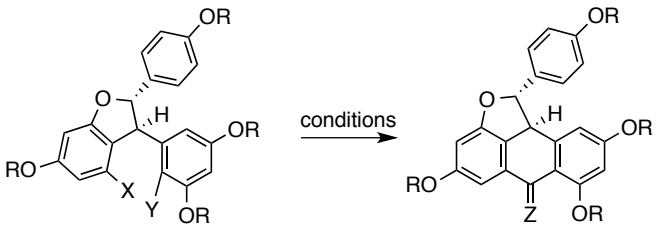


2: caraphenol A **118** **147**: α-OMe, hopeahainol E **148**: β-OMe, hopeahainol F **149**: betulifol

became apparent that the structural motif of **118** was ubiquitous with the resveratrol class in that it mapped onto countless targets. Thus its potential as a new common intermediate for oligomer synthesis became evident. The common intermediate developed previously by the Snyder

group[57] has very successfully accomplished the syntheses of natural products and it was hoped that this new intermediate could compliment the already established utility of that key structure. Elaboration of **118** towards caraphenol A has been thoroughly shown. One other particular set of natural products came to light as potential targets that could be synthesized from common intermediate **118**: hopeahainol E, F,[58] and betulifol A[59] (**147 - 149**, Scheme 35). As mentioned in Section 3.5.4, the 6,6,5 fused tricycle with one of the six membered rings being aromatic incurs a great deal of strain. Nonetheless, direct six membered ring formation was attempted by various methods as outlined in Scheme 37 with its accompanying table. No method delivered any six membered ring, normally a curious result given the general ease of making six membered rings;

Scheme 37. Direct 6-Membered Ring Formation

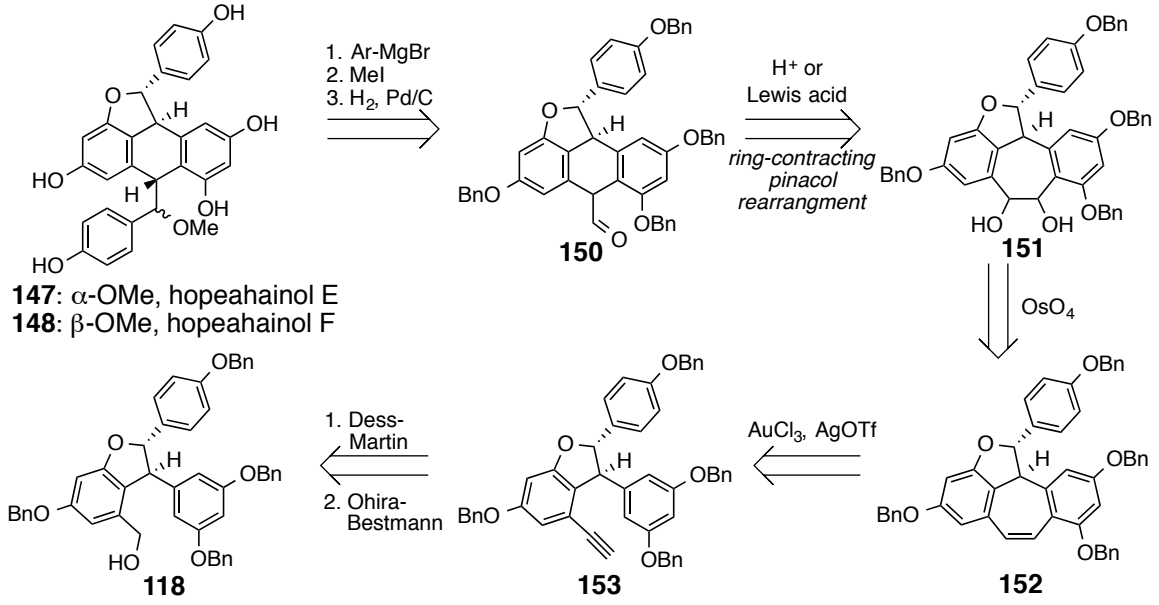


Entry	X	Y	Conditions	Result
1	-COCl	H	$AlCl_3$, CH_2Cl_2, 25 ^oC, 10 min	Decomposition
2	-COCl	H	ZnI_2, CH_2Cl_2, 25 ^oC, 12 h	No Reaction
3	-CH_2Br	H	$AlCl_3$, CH_2Cl_2, 25 ^oC, 1 h	Decomposition
4	-epoxide	H	*p*-TSA, CH_2Cl_2, 40 ^oC, 12 h	X : $CH=CH_2$
5	-epoxide	H	ZnI_2, CH_2Cl_2, 25 ^oC, 12 h	No Reaction
6	-epoxide	H	$AlCl_3$, CH_2Cl_2, 25 ^oC, 1 h	Decomposition
7	-$CH=CH_2$	H	$Hg(OTf)_2$, MeCN, 0 ^oC, 1 h, then NaCl	Trace Product
8	-$CH=CH_2$	H	*p*-TsOH, CH_2Cl_2, 100 ^oC, 12 h, sealed tube	No Reaction
9	-$CH=CH_2$	H	BDSB, $MeNO_2$, -25 ^oC, 15 min	Decomposition
10	-$CH=CH_2$	H	NBS, CH_2Cl_2, 0 ^oC, 2 h	Aryl Br
11	-CHO	Br	$CrCl_2$, $NiCl_2$, DMF, -60 ^oC to 25 ^oC, 12 h	No Reaction
12	-CHO	I	$CrCl_2$, $NiCl_2$, DMF, -60 ^oC to 25 ^oC, 12 h	No Reaction
13	-CO_2Me	Br	*n*-BuLi, THF, -78 ^oC, 1 h	Ester Addition
14	-CCH	Br	Bu_3SnH, AIBN, tol. 100 ^oC, 1 h	Hydrostannylation
15	$C(CH_2)SnBu_3$	Br	$(PPh_3)_2PdCl_2$, dioxane, 90 ^oC, 18 h	Unknown Prod.

however, accounting for the previously described strain that would be invoked for this particular system, the result is not surprising. In the sense of the reaction mechanism, the two coupling partners are rigidly kept at a "non-reactive distance" as forcing their proximity, in terms of required energy, is prohibitively expensive. If the requisite six membered ring is to form, an alternate strategy from direct cyclization must be employed.

In attempting to devise what that strategy might be, the cyclization of **93** to seven membered ring **97** (Scheme 20) was recalled. While this intermediate clearly contains as extra atom in the ring, it brings the necessary carbons for six membered ring formation into closer proximity than in the open precursor according to a model. With this in mind, it was thought that if the analogous, appropriately substituted seven membered ring alkene could be formed that perhaps a ring contraction would be more successful in delivering the natural product core given

Scheme 38. Retrosynthetic Approach to Hopeahainol E, F and Betulifol (not shown)

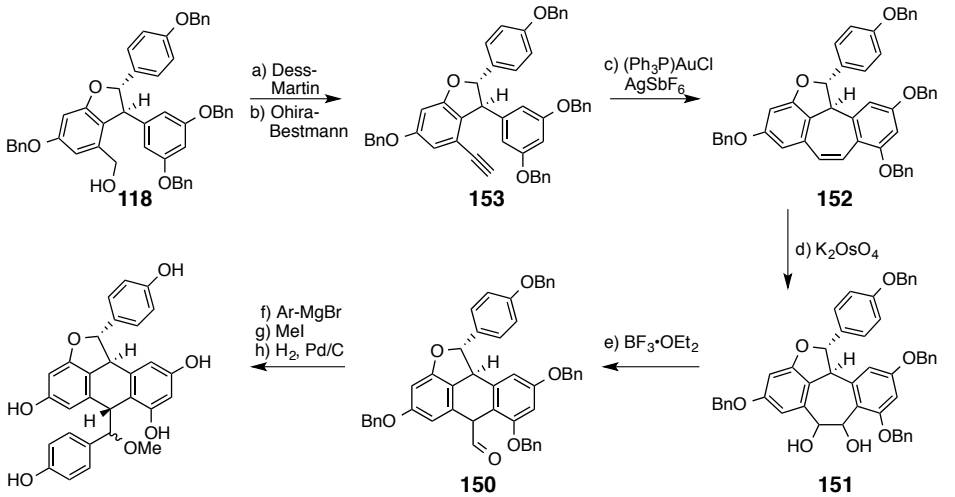


the general irreversibility of such processes and the closer proximity of the desired coupling partners as opposed to the open form structure. As shown in the full retrosynthetic analysis presented in Scheme 38, a pinacol rearrangement was chosen as the initial method for ring

contraction.[60] Beginning from the natural products, it was deemed that despite their different stereochemical array, the hopeahainols **147** and **148** as well as betulifol A **149** could derive from the same aldehyde **150** in the hope that each epimeric aldehyde could be obtained by epimerization and either thermodynamic or kinetic proton trapping. This aldehyde would be the product of a pinacol rearrangement from seven membered ring vicinal diol **151** in which step the ring contraction would take place. The matter of which hydroxyl group ionizes is inconsequential as both would lead to the same product. Diol **151** would come from is corresponding alkene **152**, the product of *7-endo-dig* cyclization of preceding alkyne **153**. Treatment of alcohol **118** with Dess-Martin periodinane, followed by the Ohira-Bestmann reagent, should furnish that alkyne **153**, with the alcohol **118** being synthesized as described in Section 3.6.

Because this retrosynthetic approach was devised during the course of the synthesis of caraphenol A, it was ultimately executed in collaboration with a graduate student Alison Gao. The final route as carried out by Ms. Gao is shown in its entirety in Scheme 39 beginning from

Scheme 39. Total Synthesis of Hopeahainols E and F.

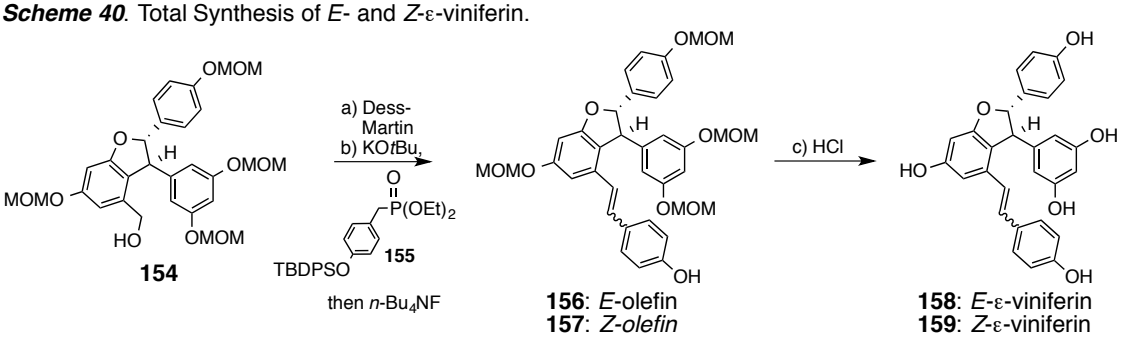


Reagents and Conditions: a) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 25 ºC, 96%; b) Ohira-Bestmann, K_2CO_3, THF/MeOH, 25 ºC, 92%; c) $(Ph_3P)AuCl$, $AgSbF_6$,DCE, 25 ºC, 99%; d) K_2OsO_4, citric acid, NMO, *t*BuOH/H_2O, 85%; e) BF_3•OEt_2, CH_2Cl_2, 0 ºC, 99%; f) 4-OBn-PhMgBr, THF, 25 ºC, 70%; g) NaH, MeI, THF, 0 ºC; h) H_2, Pd/C, EtOAc/MeOH, 25 ºC, 60% from **150**.

intermediate **118**. In the end, we were pleased to find the initial synthetic plan successful. Alison found that modified gold catalysis conditions as compared to those used before were more reliable and higher yielding. BF_3•OEt_2 was found to accomplish the ring contraction most effectively. Unfortunately, the aldehyde epimer required for the formation of betulifol A (**149**) was not accessible despite exhaustive efforts. Ultimately, an efficient synthesis of hopeahainols E and F (**147** and **148**) was completed.

From this intermediate numerous and challenging carbon frameworks are accessible either directly or indirectly. Without a great deal of imagination, a total synthesis of *E*- and *Z*-ε-viniferin (**158**, **159**) could be realized as shown in Scheme 40.[61] Although final deprotection of

Scheme 40. Total Synthesis of *E*- and *Z*-ε-viniferin.

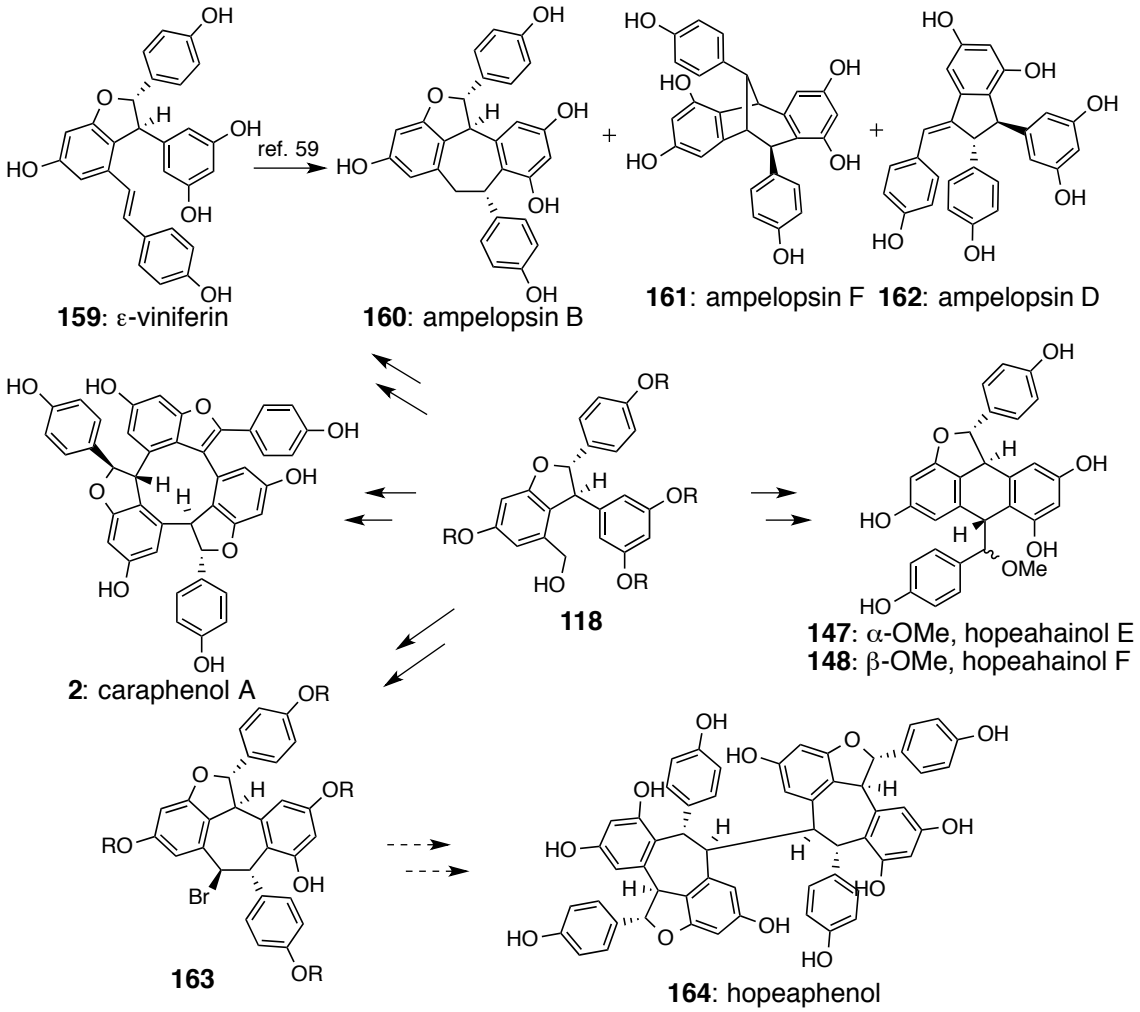


Reagents and Conditions: a) Dess-Martin periodinane, CH_2Cl_2, 25 ºC, 1 h, 87%; b) KO*t*Bu, **155**, -78 ºC, 3 h, then *n*-Bu_4NF, 25 ºC, 12 h, 52% *E*-, 18% *Z*- separable by flash chormatrography and carried forward separately; c) HCl, THF/MeOH, 25 ºC, 4 h, 74% for *E*-ε-viniferin, 84% for *Z*-ε-viniferin.

benzyl ethers proved problematic, methoxymethyl (MOM) ethers were suitable for the final unveiling giving both *E*- (**158**) and *Z*-ε-viniferin (**159**). When coupled with the knowledge contributed by Takaya *et al.* that ε-viniferin can be transformed into ampelopsins A, B, D, and F (**160**-**162**, ampelopsin A not shown), the power of this intermediate becomes abundantly greater for the synthesis of various scaffolds (Scheme 41).[62] From protected ε-viniferin as obtained through common intermediate **118**, another member of the Snyder lab, Maria Chiriac, has accomplished the synthesis of seven membered ring bromide **163**. Efforts towards radical

homocoupling are underway and, if successful, would lead to increasingly complex architectures such as hopeaphenol (**164**).[63]

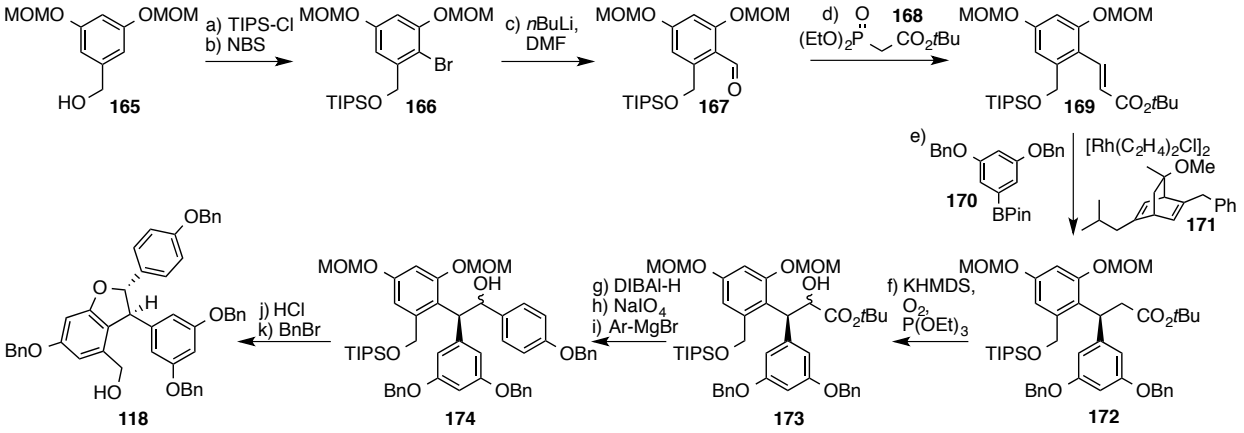
Scheme 41. Scope of Common Intermediate **118**.



While this novel, common intermediate allows access to a number of frameworks inaccessible by other methods, still lacking at this stage was a general asymmetric solution to resveratrol synthesis. Two members of the Snyder group, Jonathan Boyce and Adam Levinson, had previously developed an asymmetric approach to select members of the resveratrol oligomeric family (not shown). Seeing that a simple modification of their substrates could produce an enantio-enriched route to the common intermediate **118**, Adam Levinson was tasked

with applying their method to this system. The successful accomplishment of that goal is shown in Scheme 42, with enantioinduction taking place in the form of a Michael addition of an aryl

Scheme 42. Asymmetric Synthesis of Common Intermediate **118**.



Reagents and Conditions: a) TIPS-Cl, imid., DMF, 25 ºC, 1 h, 97%; b) NBS, CH_2Cl_2, 0 ºC, 1 h, 94%; c) *n*BuLi, THF, -78 ºC, 20 min, then DMF, 25 ºC, 5 h, 59%; d) **168**, DBU, LiCl, MeCN, reflux, 30 min, 84%; e) **170**, **171**, $[Rh(C_2H_4)_2Cl]_2$, KOH,1,4-dioxane, 80 ºC, 1 h, 81%, 91% *ee;* f) KHMDS, O_2, $P(OEt)_3$, THF, -50 ºC, 35 min, 76%; g) DIBAl-H, THF, 0 ºC, 2.5 h; h) $NaIO_4/SiO_2$, CH_2Cl_2, 25 ºC, 45 min; i) 4-OBn-PhMgBr, THF, 25 ºC, 30 min, 89% from **173**; j) HCl, MeOH, 40 ºC, 2 h, 56%; k) BnBr, K_2CO_3, acetone, reflux, 5 h, 82%.

boronic acid **170** to unsaturated ester **169**.[64] Not only does this route provide an effective method for the asymmetric synthesis of **118**, it formally renders all of the syntheses shown in Scheme 41 as enantioselective. We are excited to see the future of this compound as a common intermediate and a general solution for asymmetric resveratrol oligomer synthesis.

3.10 Conclusion

Highly advanced and complex intermediates were synthesized for the exploration of all carbon, nine membered ring synthesis as part of a drive to construct oligomeric, resveratrol-based natural products. Careful analysis of the gold-catalyzed activation of an alkyne for Friedel-Crafts cyclization provided invaluable knowledge regarding the conformational and reactive tendencies of the system in question. This exploration allowed for the identification of a substrate poised for a successful cyclization and, upon submitting that substrate to said conditions, we accomplished the first ever reported *9-exo-dig* cyclization. Modification of this

approach led to an alternate cyclization that enabled the first total synthesis of caraphenol A to be achieved. This synthesis was accomplished in a longest linear sequence of 23 steps with an overall yield of 7.8% and an average yield 89.5% per step. Each step was executed on at least a gram scale with >600 mg of the target molecule obtained, by far the largest amount of any resveratrol-based trimer ever synthesized. This material will soon be submitted for exhaustive biological evaluation in collaborative efforts seeking to establish its range of potential bioactivity. Furthermore, new common intermediate was identified and in addition to caraphenol A was elaborated to *E*- and *Z*-ε-viniferin and hopeahainols E and F, with the potential for many other structures in the future. Formally, the synthesis of *E*-ε-viniferin also constitutes the synthesis of ampelopsins A, B, D, and F. An asymmetric variant of this intermediate was accessed by fellow group members accomplishing the formally asymmetric synthesis of all natural products listed above as well as the first general, asymmetric solution to the oligomeric resveratrol family.

Acknowledgments

Ms. Alison Gao is thanked for carrying out the synthetic approach towards hopeahainols E and F and for providing some supplies of previously prepared synthetic intermediates. Mr. Jonathan Boyce and Mr. Adam Levinson are thanked for developing an asymmetric approach towards resveratrol based frameworks and applying it to the new common intermediate. Prof. Gerard Parkin and Dr. Joshua Palmer are thanked for X-ray crystallographic analysis of noted intermediates. Dr. Yasuhiro Itagaki is acknowledged for mass spectrometric analysis. Dr. John Decatur and Mr. Michael Appel are acknowledged for NMR assistance.

3.11 References

1. (a) R. J. Pryce, P. Langcake, *Phytochemistry* **1977**, *16*, 1452 - 1454; (b) H.-F. Luo, L.-P. Zhang, C.-Q. Hu, *Tetrahedron* **2001**, 4849 - 4854; (c) Y. Shirataki, T. Tanaka, M. Ohyama, A. Toda, M. Iinuma, *Natural Medicines* **2002**, *56*, 139 - 142; (d) H.-X. Liu, W.-H. Lin, J.-S. Yang, *Chem. Pharm. Bull.* **2004**, *52*, 1339 - 1341; (e) S. Wang, D. Ma, C. Hu, *Helv. Chim. Acta* **2005**, *88*, 2315 - 2321; (f) T. Ito, T. Tanaka, Y. Ido, K.-I. Nakaya, M. Iinuma, S. Riswan, *Chem. Pharm. Bull.* **2000**, *48*, 1001 - 1005; (g) T. Ito, N. Abe, M. Oyama, T. Tanaka, J. Murata, D. Darnaedi, M. Iinuma, *Helv. Chim. Acta* **2009**, *92*, 1203 - 1216; (h) T.-M. Wang, K.-J. Wang, J. Tang, N. Li, *J. Chin. Chem. Soc.* **2009**, *56*, 881 - 884; (i) H. M. Ge, B. Huang, S. H. Tan, D. H. Shi, Y. C. Song, R. X. Tan, *J. Nat Prod.* **2006**, *69*, 1800 - 1802; (j) H. M. Ge, W. H. Yang, Y. Shen, N. Jiang, Z. K. Guo, Q. Luo, Q. Xu, J. Ma, R. X. Tan, *Chem. Eur. J.* **2010**, *16*, 6338 - 6345; (k) K. Suzuki, T. Shimizu, J. Kawabata, J. Mizutani, *Agric. Biol. Chem.* **1987**, *51*, 1003 - 1008; (l) J. Kawabata, M. Mishima, H. Kurihara, J. Mizutani, *Phytochemistry* **1995**, *40*, 1507 - 1510.

2. R. A. Hansen, G. Gartlehner, D. J. Kaufer, K. N. Lohr, T. Carey, *Drug Class Review on Alzheimer's Drugs* **2006**. Final Report.

3. B. M. McGleenon, K. B. Dynan, A. P. Passmore, *Br. J. Clin. Pharmacol.* **1999**, *48*, 471 - 480.

4. A. H. Sung, S. Y. Kang, K. Y. Lee, M. J. Park, J. H. Kim, J. H. Park, Y. C. Kim, J. Kim, Y. C. Kim, *Biol. Pharm. Bull.* **2002**, *25*, 125 - 127.

5. T. Yan. T. Wang, W. Wei, N. Jiang, Y. H. Qin, R. X. Tan, H. M. Ge, *Planta Med.* **2012**, *78*, 1015 - 1019.

6. D. H. Kim, S.-H. Kim, H. J. Kim, C. Jin, K. C. Chung, H. Rhim, *Biol. Pharm. Bull.* **2010**, *33*, 2024 - 2028.

7. E. Y. Chung, B. H. Kim, M. K. Lee, Y.-P. Yun, S. H. Lee, K. R. Min, Y. Kim, *Planta Med.* **2003**, *69*, 710 - 714.

8. J. Y. Lee, J.-H. Kim, S. S. Kang, C. S. Bae, S. H. Choi, *Am. J. Chin. Med.* **2004**, *32*, 521 - 530.

9. E. Y. Chung, E. Roh, J.-A. Kwak, H.-S. Lee, S. H. Lee, C.-K. Lee, S.-B. Han, Y. Kim, *J. Pharmacol. Sci.* **2010**, *112*, 405 - 414.

10. S. A. Chowdhury, K. Kishino, R. Satoh, K. Hashimoto, H. Kikuchi, H. Nishikawa, Y. Shirataki, H. Sakagami, *Anticancer Res.* **2005**, *25*, 2055 - 2064.

11. M. Munoz, M. Henderson, M. Haber, M. Norris, *IUBMB Life* **2007**, *59*, 752 - 757.

12. M. Bobrowska-Hagerstrand, M. Lillas, L. Mrowczynska, A. Wrobel, Y. Shriataki, N. Motohashi, H. Hagerstrand, *Anticancer Res.* **2006**, *26*, 2081 - 2084.

13. Romeo, John T.; (1999). *Phytochemicals in Human Health Protection, Nutrition, and Plant Defense*. Springer.

14. P. Kulanthaivel, W. P. Janzen, L. M. Ballas, J. B. Jiang, C.-Q. Hu, J. W. Darges, J. C. Seldin, D. J. Cofield, L. M. Adams, *Planta Med.* **1995**, *61*, 41 - 44.

15. S. A. Snyder, S. B. Thomas, A. C. Mayer, S. P. Breazzano, *Angew. Chem. Int. Ed.* **2012**, *51*, 4080 - 4084.

16. (a) Smith, Michael B.; March, Jerry; (2007). *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (6th ed.)*. Hoboken, N. J.: John Wiley and Sons, Inc.; (b) Anslyn, Eric V.; Dougherty, Dennis A.; (2005). *Modern Physical Organic Chemistry*. Sausalito, CA: University Science Books.

17. R. H. Grubbs, *Tetrahedron* **2004,** *60*, 7117 – 7140.

18. C. Hamel, E. V. Prusov, J. Gertsch, B. Schweizer, K.-H. Altmann, *Angew. Chem. Int. Ed.* **2008**, *47*, 10081 - 10085.

19. Y. Li, K. J. Hale, *Org. Lett.* **2007**, *9*, 1267 - 1270.

20. K. C. Nicolaou, A. L. Smith, E. W. Yue, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5881 - 5888.

21. A. G. Myers, M. Hammond, Y. Wu, J.-N. Xiang, P. M. Harrington, E. Y. Kuo, *J. Am. Chem. Soc.* **1996**, *118*, 10006 - 10007.

22. K. Komano, S. Shimamura, M. Inoue, M. Hirama, *J. Am. Chem. Soc.* **2007**, *129*, 14184 - 14186.

23. (a) K. Ogawa, Y. Koyama, I. Ohashi, I. Sato, M. Hirama, *Chem. Commun.* **2008**, 6327 - 6329; (b) M. Hirama, K. Fujiwara, K. Shigematu, Y. Fukazawa, *J. Am. Chem. Soc.* **1989**, *111*, 4120 - 4122.

24. C. A. Grob, W. Baumann, *Helv. Chim. Acta* **1955**, *38*, 594.

25. E. J. Corey, R. B. Mitra, H. Uda, *J. Am. Chem. Soc.* **1964**, *86*, 485 - 492.

26. L. A. Paquette, J. Yang, Y. O. Long, *J. Am. Chem. Soc.* **2002**, *124*, 6542 - 6543.

27. C. Friedel, J. M. Crafts, *Compt. Rend.* **1877**, *84*, 1392 & 1450.

28. (a) F. E. Ziegler, P. A. Zoretic, *Tet. Lett.* **1968**, *22*, 2639 - 2641; (b) F. E. Ziegler, J. A. Kloek, P. A. Zoretic, *J. Am. Chem. Soc.* **1969**, *91*, 2342 - 2346.

29. A. H. Jackson, P. Smith, *Chem. Commun.* **1967**, 264 - 266.

30. Y. M. Vargas-Rodriguez, M. Vargas, R. Miranda, B. Francisco, O. Noguez, J. A. Morales-Serna, M. Salmon, *Org. Commun.* **2012**, *5*, 58 - 63.

31. P. H. Gore, *Chem. Rev.* **1955**, *55*, 229 - 281.

32. S. A. Snyder, A. Gollner, M. I. Chiriac, *Nature* **2011**, *474*, 461 - 466.

33. (a) S. J. O'Malley, K. L. Tan, A. Watzke, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2005**, *127*, 13496 - 13497; (b) D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 5767 - 5769.

34. D. B. Dess, J. C. Martin *J. Org. Chem.* **1983**, *48*, 4155 - 4156.

35. As an example of the classical use of this method in total synthesis see: J. R. Beck, R. N. Booher, A. C. Brown, R. Kwok, A. Pohland, *J. Am. Chem. Soc.* **1967**, *89*, 3934.

36. E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353 - 1364.

37. a) S. E. Snyder, F. A. Aviles-Garay, R. Chakraborti, D. E. Nichols, V. J. Watts, R. B. Mailman, *J. Med. Chem.* **1995**, *38*, 2395 – 2409; b) N. J. Bach, E. C. Kornfeld, N. D. Jones, M. O. Chaney, D. E. Dorman, J. W. Paschal, J. A. Clemens, E. B. Smalstig, *J. Med. Chem.* **1980**, *23*, 481 – 491.

38. B. O. Lindgren, T. Nilsson, *Acta Chem. Scan.* **1973**, *27*, 888 – 890.

39. K. Fries, G. Finck, *Chem. Ber.* **1908**, *41*, 4271 - 4284.

40. K. C. Nicolaou, K. Koide, M. E. Bunnage, *Chem. Eur. J.* **1995**, *1*, 454.

41. F. Mattivi, U. Vshovsek, G. Malacarne, D. Masuero, L. Zulini, M. Stefanini, C. Moser, R. Velasco, G. Guella, *J. Agric. Food Chem.* **2011**, *59*, 5364 - 5375.

42. L. Horner, H. M. R. Hoffmann, H. G. Wippel, *Chem. Ber.* **1958**, *91*, 61 - 63.

43. S. Koerbe, D. B. Sowers, A. Franken, J. Michl, *Inorg. Chem.* **2004**, *43*, 8158 - 8161.

44. A. W. Jones, T. D. Wahyuningsih, K. Pchalek, N. Kumar, D. StC. Black, *Tetrahedron* **2005**, *61*, 10490 - 10500.

45. N. D. Shapiro, F. D. Toste, *Synlett* **2010**, *5*, 675 - 691.

46. S. Muller, B. Liepold, G. Roth, H. J. Bestmann, *Synlett* **1996**, *6*, 521 - 522.

47. V. Mamane, P. Hannen, A. Furstner, *Chem. Eur. J.* **2004**, *10*, 4556 - 4575.

48. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734 - 736.

49. Z. Shi, C. He, *J. Org. Chem.* **2004**, *69*, 3669 - 3671.

50. (a) G. S. Hammond, *J. Am. Chem. Soc.* **1955**, *77*, 334 - 338; (b) Carey, F.A.; Sundberg, R.J. (1990). *Advanced Organic Chemistry.-Part A: Structure and Mechanism*. New York, NY: Plenum.

51. (a) M. T. Reetz, K. Sommer, *Eur. J. Org. Chem.* **2003**, 3485 - 3496; (b) K. Surendra, W. Qiu, E. J. Corey, *J. Am. Chem. Soc.* **2011**, *133*, 9724 - 9726.

52. For an example of atropisomer equilibration and recycling see: D. L. Boger, S. Miyazaki, S. H. Kim, J. H. Wu, O. Loiseleur, S. L. Castle, *J. Am. Chem. Soc.* **1999**, *121*, 3226 - 3227.

53. H. Ishii, S. Ohta, H. Nishioka, N. Hayashida, T. Harayama, *Chem. Pharm. Bull.* **1993**, *41*, 1166 - 1168.

54. H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483 - 2547.

55. O. Mitsunobu, Y. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380 - 2382.

56. L. Lemigre, F. Lesetre, J.-C. Combret, J. Maddaluno, *Tetrahedron* **2004**, *60*, 415 - 427.

57. (a) S. A. Snyder, A. L. Zografos, Y. Lin, *Angew. Chem. Int. Ed.* **2007**, *46*, 8186 - 8191; (b) S. A. Snyder, S. P. Breazzano, A. G. Ross, Y. Lin, A. L. Zografos, *J. Am. Chem. Soc.* **2009**, *131*, 1753 - 1765.

58. H.-M. Ge, W.-H. Yang, J. Zhang, R.-X. Tan, *J. Agric. Food Chem.* **2009**, *57*, 5756 - 5761.

59. W. Li, B. Li, Y. Chen, *Phytochemistry* **1998**, *49*, 1393 - 1394.

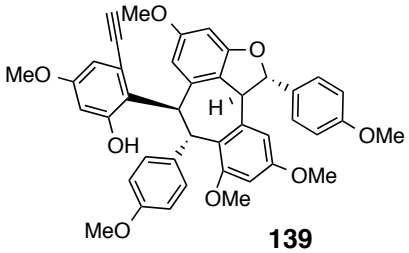
60. X. Chen, L. Esser, P. G. Harran, *Angew. Chem. Int. Ed.* **2000**, *39*, 937 - 940.

61. A. E. Bala, A. Kollmann, P.-H. Ducrot, A. Majira, L. Kerhoas, R. Delorme, J. Einhorn, *Pestic. Sci.* **1999**, *55*, 197 - 218.

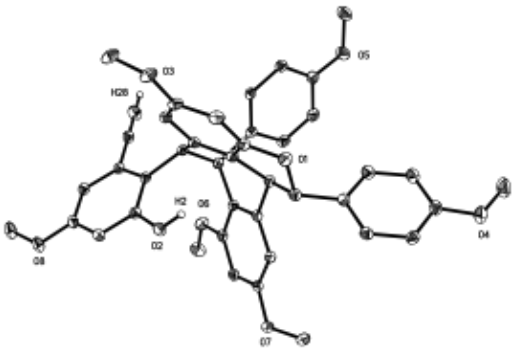
62. Y. Takaya, K.-X. Yan, K. Terashima, J. Ito, M. Niwa, *Tetrahedron* **2002**, *58*, 7259 - 7265.

63. P. Coggon, N. F. Janes, F. E. King, T. J. King, R. J. Molyneux, J. W. W. Morgan, K. Sellars, *J. Chem. Soc.* **1965**, 406 - 409.
64. K. Lukin, Q. Zhang, M. R. Leanna, *J. Org. Chem.* **2009**, *74*, 929 - 931.

Relevent X-Ray Crystal Structures:



139



3.12 Experimental Procedures

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), acetonitrile (MeCN), toluene, benzene, diethyl ether (Et_2O) and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and either an aqueous solution of ceric ammonium sulfate and ammonium molybdate and heat or an aqueous solution of potassium permanganate and sodium bicarbonate and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-300, DRX-400, DMX-500 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, br = broad, AB = AB quartet, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using the MALDI (matrix-assisted laser-desorption ionization) technique.

Bromide 50. $LiAlH_4$ (6.25 g, 165 mmol, 1.5 equiv) was added portionwise to a solution

of **49** (20.0 g, 110 mmol, 1.0 equiv) in THF (250 mL) at 25 °C in an ambient atmosphere. After stirring for 5 min at 25 °C, the reaction mixture was quenched by the careful dropwise addition of water (10 mL), followed by saturated aqueous sodium potassium tartrate (400 mL) and stirring of the resultant solution vigorously for 1 h. The reaction mixture was then poured into water (100 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layers were wash with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated with give the desired benzylic alcohol (18.5 g, 99% yield) as a white solid. Pressing forward without any further purification, the newly formed benzylic alcohol (18.5 g, 110 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (300 mL), cooled to 0 °C, and NBS (19.6 g, 110 mmol, 1.0 equiv) was added portionwise over the course of 30 min. The reaction mixture was then warmed to 25 °C and stirred for 12 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (100 mL), poured into water (50 mL), and extracted (3 × 200 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 × 100 mL), dried ($MgSO_4$), filtered and concentrated to give resulting bromide (25.8 g, 95% yield) as a white solid. To a solution of the newly formed bromide (19.0 g, 76.9 mmol, 1 equiv) in CH_2Cl_2 (400 mL) was added iodine (39.0 g, 153.8 mmol, 2.0 equiv), 1-methylimidazole (12.3 mL, 153.8 mmol, 2.0 equiv), and triispropylsilyl chloride (19.5 mL, 92.3 mmol, 1.2 equiv) at 25 °C . After stirring the resultant solution for 1 h, the CH_2Cl_2 was removed by rotary evaporation, the crude mixture taken up in EtOAc (300 mL), and washed with saturated aqueous Na_2SO_3 (200 mL), brine (150 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 98:2) to give **50** (29.2 g, 95% yield) as a pale yellow oil. **50**: R_f = 0.75 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2941, 2891, 2865, 1588, 1455, 1433, 1419, 1368, 1328, 1288, 1220, 1199, 1156, 1128, 1077, 1061, 1023, 996, 955, 923,

881, 836, 806, 682, 644, 592, 550, 521, 500, 461; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 2.8 Hz, 1 H), 6.41 (d, *J* = 2.8 Hz, 1 H), 4.81 (s, 2 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 1.22 (m, 3 H), 1.12 (d, *J* = 6.7 Hz, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 156.2, 142.9, 103.5, 100.6, 98.4, 65.2, 56.4, 55.6, 18.2, 12.2; HRMS (FAB+) calcd for $C_{18}H_{30}O_3SiBr^+$ [M^+] 401.1148, found 401.1147.

Ketone 51. *n*-BuLi (19.5 mL, 1.6 M in THF, 31.2 mmol, 1.4 equiv) was added slowly over the course of 5 min to a solution of **50** (8.93 g, 22.1 mmol, 1.0 equiv) in THF (200 mL) at –78 °C. After stirring the resultant solution at –78 °C for 20 min, a solution of 3,5-dimethoxybenzaldehyde (5.99 g, 36.1 mmol, 1.6 equiv) in THF (50 mL) was added slowly at –78 °C via cannula, and the resultant mixture was stirred at –78 °C for 1 h. The reaction contents were then warmed slowly to 25 °C, and stirred for an additional 8 h. Upon completion, the reaction contents were quenched with saturated aqueous NH_4Cl (100 mL), poured into water (50 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layers were then washed with brine (100 mL), dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 23:2) to give the desired alcohol (9.79 g, 90%) as a yellow oil. Pressing forward, to a solution of this newly synthesized alcohol (9.79 g, 20.0 mmol, 1.0 equiv) in CH_2Cl_2 (120 mL) at 25 °C was sequentially added $NaHCO_3$ (16.8 g, 199.5 mmol, 10.0 equiv) and Dess–Martin periodinane (9.31 g, 22.0 mmol, 1.2 equiv), and the resultant mixture was stirred at 25 °C for 30 min in an ambient atmosphere. Upon completion, saturated aqueous Na_2SO_3 (50 mL) was added and the reaction contents were stirred vigorously at 25 °C for 5 min. Upon completion, the reaction mixture was then poured into water (50 mL) and extracted with EtOAc (3 × 120 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica

gel, hexanes/EtOAc, 19:1→23:2) to give **51** (7.42 g, 76% yield) as a yellow oil. **51**: R_f = 0.69 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2941, 2865, 1667, 1590, 1456, 1425, 1350, 1320, 1298, 1201, 1153, 1123, 1062, 989, 927, 882, 842, 825, 800, 770, 742, 681, 657, 597, 538, 500; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 2.4 Hz, 2 H), 6.90 (d, *J* = 2.2 Hz, 1 H), 6.63 (t, *J* = 2.3 Hz, 1 H), 6.40 (d, *J* = 2.2 Hz, 1 H), 4.66 (s, 2 H), 3.86 (s, 3 H), 3.78 (s, 6 H), 3.65 (s, 3 H), 1.01 (m, 21 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 161.9, 160.9, 158.3, 142.8, 140.5, 119.2, 107.1, 105.8, 103.0, 97.3, 62.5, 55.9, 55.7, 55.5, 18.1, 12.1; HRMS (FAB+) calcd for $C_{27}H_{41}O_6Si^+$ [M^+] 489.2672, found 489.2679.

Ketone 52. BCl_3 (16.6 mL, 1.0 M in CH_2Cl_2, 16.6 mmol, 1.1 equiv) was added to a solution of **51** (7.4 g, 15.2 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) at 25 °C. After stirring for 10 min at 25 °C, the reaction contents were quenched by the slow, careful addition of saturated aqueous $NaHCO_3$ (50 mL), poured into water (30 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated to give the desired monophenol intermediate **S1** (7.20 g, quantitative yield assumed) as a brown oil which was carried on without further purification. **S1**: R_f = 0.66 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2941, 2865, 1588, 1456, 1425, 1348, 1317, 1297, 1241, 1204, 1154, 1110, 1063, 1012, 990, 947, 927, 882, 841, 800, 716, 681, 615, 536, 501, 460; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.07 (s, 1H), 6.82 (d, *J* = 2.6 Hz, 1 H), 6.65 (d, *J* = 2.3 Hz, 2 H), 6.59 (t, *J* = 2.3 Hz, 1 H), 6.43 (d, *J* = 2.6 Hz, 1 H), 4.33 (s, 2 H), 3.86 (s, 3 H), 3.78 (s, 6 H), 0.92 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 165.1, 164.1, 161.2, 145.9, 143.5, 122.9, 106.8, 105.5, 104.2, 99.9, 64.1, 55.7, 55.6, 18.0, 11.9; HRMS (FAB+) calcd for $C_{26}H_{39}O_6Si^+$ [M^+] 475.2516, found 475.2542. Pressing forward, crude monophenol **51** (7.20 g, 15.2 mmol, 1.0 equiv) was dissolved in acetone

(100 mL) at 25 °C and K_2CO_3 (10.5 g, 75.9 mmol, 5 equiv), benzyl bromide (3.6 mL, 30.4 mmol, 2.0 equiv) and *n*-Bu_4NI (0.560 g, 1.52 mmol, 0.1 equiv) were added sequentially in an ambient atmosphere. The reaction flask was then warmed to 56 °C and stirred for 12 h. Upon completion, the reaction contents were quenched by the addition of water (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 19:1) to afford ketone **52** (7.03 g, 82% yield from **51**) as a yellow oil. **52**: R_f = 0.72 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2941, 2865, 1665, 1590, 1456, 1427, 1381, 1348, 1318, 1299, 1235, 1203, 1194, 1152, 1123, 1057, 988, 925, 882, 842, 824, 797, 771, 737, 679, 658, 603, 533, 500, 461; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 3 H), 6.96 (d, *J* = 2.2 Hz, 1 H), 6.94 (m, 2 H), 6.92 (d, *J* = 2.4 Hz, 2 H), 6.63 (t, *J* = 2.3 Hz, 1 H), 6.42 (d, *J* = 2.2 Hz, 1 H), 4.92 (s, 2 H), 4.74 (s, 2 H), 3.84 (s, 3 H), 3.76 (s, 6 H), 1.05 (m, 21 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 161.9, 160.9, 157.5, 143.4, 141.3, 136.6, 128.4, 127.8, 127.0, 119.4, 107.0, 105.7, 103.4, 98.5, 70.3, 62.6, 55.7, 55.5, 18.1, 12.1; HRMS (FAB+) calcd for $C_{33}H_{45}O_6Si^+$ [M^+] 565.2985, found 565.2974.

Aldehyde 54. To a suspension of trimethylsulfonium iodide (25.4 g, 124.4 mmol, 10.0 equiv) in THF (300 mL) at 0 °C was added *n*-BuLi (62.2 mL, 1.6 M in hexanes, 99.5 mmol, 8.0 equiv). After stirring the resulting opaque pale yellow solution at 0 °C for 4 min, a solution of **52** (7.03 g, 12.4 mmol, 1.0 equiv) in THF (80 mL) was added via cannula over the course of 5 min. The reaction mixture was then warmed to 25 °C and stirred for 1 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (150 mL), poured into water (50 mL), and extracted with EtOAc (3 × 200 mL). The combined organic layers were then washed with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated. Pressing forward

without any further purification, the so-obtained crude epoxide was taken up in benzene (100 mL) and ZnI_2 (3.97 g, 12.4 mmol, 1.0 equiv) was added as a single portion at 25 °C in an ambient atmosphere. Upon completion (generally 10–15 min as judged by careful TLC analysis), the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL), poured into water (100 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated to give the desired aldehyde **54** (7.20 g, 12.4 mmol, quantitative yield assumed) as a yellow oil. Generally, this material was carried forward without any further purification. However, a pure sample for characterization could be obtained by flash column chromatography (silica gel, hexanes/EtOAc, 23:2), affording the aldehyde as a yellow oil. **54**: R_f = 0.72 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2941, 2865, 1720, 1594, 1457, 1428, 1382, 1319, 1203, 1194, 1149, 1057, 995, 923, 882, 840, 739, 685, 658, 540, 501, 461; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1 H), 7.31–7.25 (m, 5 H), 6.84 (d, *J* = 2.4 Hz, 1 H), 6.52 (d, *J* = 2.4 Hz, 1 H), 6.34 (t, *J* = 1.7 Hz, 1 H), 6.33 (d, *J* = 2.0 Hz, 2 H), 5.03 (s, 2 H), 4.83 (d, *J* = 9.4 Hz, 1 H), 4.74 (s, 1 H), 4.61 (d, *J* = 9.4 Hz, 1 H), 3.80 (s, 3 H), 3.68 (s, 6 H), 1.03 (m, 21 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 161.0, 160.3, 156.9, 143.2, 139.4, 136.4, 128.7, 128.1, 127.6, 116.4, 107.1, 104.8, 99.3, 99.1, 70.9, 63.5, 56.3, 55.4, 55.3, 18.1, 12.1; HRMS (FAB+) calcd for $C_{34}H_{45}O_6Si^+$ [M^+] 577.2985, found 577.2960.

Alcohols 55/56. Next, the crude aldehyde **54** (7.20 g, 12.4 mmol, 1.0 equiv) was dissolved in THF (100 mL) and 4-benzyloxyphenylmagnesium bromide (15.0 mL, 1.0 M in THF, 15.0 mmol, 1.2 equiv) was added at 25 °C. After stirring at 25 °C for 10 min, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (30 mL), poured into water (20 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were then

washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant crude material by flash column chromatography (silica gel, hexanes/EtOAc, 23:2→9:1) gave benzylic alcohols **55/56** (9.05 g, 95% yield from **52**, 1:1 mixture of diastereomers) as a yellow oil.

Dihydrobenzofurans 60 and 61. To a solution of benzylic alcohols **55/56** (9.05 g, 11.9 mmol, 1.0 equiv) in EtOAc (60 mL) at 25 °C was sequentially added 10% Pd/C (3.79 g, 3.56 mmol, 0.3 equiv Pd), $NaHCO_3$ (0.300 g, 3.56 mmol, 0.3 equiv), and MeOH (60 mL). H_2 gas was then bubbled through the reaction mixture for 30 min, after which time the reaction contents were stirred at 25 °C under a H_2 atmosphere (1 atm) for 4 h. Upon completion, the reaction mixture was filtered by vacuum filtration using filter paper (Whatman 1) and a Buchner funnel. The filtrate was concentrated, dissolved in CH_2Cl_2 (100 mL), and *p*-toluenesulfonic acid (2.26 g, 11.9 mmol, 1.0 equiv) was added. The resultant solution was then stirred at 25 °C in an ambient atmosphere for 30 min, after which time the reaction contents were quenched by the slow, careful addition of saturated aqueous $NaHCO_3$ (50 mL), poured into water (30 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude product **59** was dissolved in acetone (80 mL) at 25 °C, and K_2CO_3 (6.56 g, 47.4 mmol, 4 equiv) and MeI (1.48 mL, 23.7 mmol, 2.0 equiv) were added sequentially in an ambient atmosphere. The reaction flask was then warmed to 56 °C and the contents were stirred for 4 h. Upon completion, the reaction mixture was quenched by the addition of water (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) to afford the desired permethylated material (6.63 g, 97% yield from **55/56**) as a yellow foam.

Pressing forward, this newly synthesized material (6.63 g, 11.5 g, 1.0 equiv) was dissolved in THF (60 mL) and treated with TBAF (12.6 mL, 1.0 M in THF, 12.6 mmol, 1.1 equiv) at 25 °C. After stirring the reaction contents at 25 °C for 1 h, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (30 mL), poured into water (20 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were then washed with brine (40 mL), dried ($MgSO_4$), concentrated, and purified by flash column chromatrography (silica gel, hexanes/EtOAc, 4:1) to give **60** (4.15 g, 86% yield) as a pale yellow foam along with the *cis*-disposed dihydrofuran (**61**, 0.445 g, 9.2% yield). [Note: Solid $NaHCO_3$ was used in the hydrogenation to buffer the relatively high acidity of the palladium catalyst used. The progress of this hydrogenation varied heavily with different bottles of palladium catalyst and needed to be reinvestigated with each new commercial bottle.] **60**: R_f = 0.38 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3422, 2939, 2839, 1702, 1593, 1514, 1461, 1429, 1357, 1305, 1248, 1203, 1176, 1154, 1132, 1060, 1035, 986, 927, 882, 830, 776, 756, 693, 619, 536, 500; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 6.53 (d, *J* = 2.3 Hz, 1 H), 6.48 (d, *J* = 2.2 Hz, 1 H), 6.37 (t, *J* = 2.2 Hz, 1 H), 6.31 (d, *J* = 2.3 Hz, 2 H), 5.49 (d, *J* = 6.3 Hz, 1 H), 4.43 (d, *J* = 6.4 Hz, 1 H), 4.28 (dd, *J* = 13.5, 4.4 Hz, 1 H), 4.23 (dd, *J* = 13.5, 4.5 Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.73 (s, 6 H), 1.47 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 161.4, 159.7, 145.5, 138.8, 133.6, 127.0, 119.0, 114.2, 105.9, 105.7, 99.0, 95.4, 93.4, 62.6, 56.7, 55.7, 55.5, 55.4; HRMS (FAB+) calcd for $C_{25}H_{26}O_6^+$ [M^+] 422.1729, found 422.1757. **61**: R_f = 0.28 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3437, 3000, 2937, 2838, 1800, 1594, 1515, 1490, 1462, 1441, 1429, 1346, 1300, 1248, 1203, 1175, 1147, 1134, 1065, 1037, 979, 937, 836, 784, 734, 691, 647, 540; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.7 Hz, 2 H), 6.66 (d, *J* = 8.7 Hz, 2 H), 6.56 (d, *J* = 2.1 Hz, 1 H), 6.53 (d, *J* = 2.1 Hz, 1 H), 6.11 (t, *J* = 2.2 Hz, 1 H), 5.93 (d, *J* =

8.5 Hz, 1 H), 5.81 (d, *J* = 2.2 Hz, 2 H), 4.63 (d, *J* = 8.5 Hz, 1 H), 4.39 (dd, *J* = 12.5, 4.7 Hz, 1 H), 4.33 (d, *J* = 13.1 Hz, 1 H), 3.84 (s, 3 H), 3.71 (s, 3 H), 3.55 (s, 6 H), 1.45 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 161.4, 160.5, 159.0, 141.7, 138.8, 129.3, 127.9, 120.2, 113.2, 107.3, 105.9, 98.8, 95.7, 89.6, 63.0, 55.7, 55.3, 55.3, 52.1; HRMS (FAB+) calcd for $C_{25}H_{26}O_6^+$ [M^+] 422.1729, found 422.1727.

Ester 75. $NaHCO_3$ (2.39 g, 28.4 mmol, 10.0 equiv) and Dess–Martin periodinane (1.33 g, 3.12 mmol, 1.1 equiv) were added sequentially to a solution of **60** (1.22 g, 2.89 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at 25 °C, and the resultant mixture was stirred for 30 min in an ambient atmosphere. Upon completion, saturated aqueous Na_2SO_3 (20 mL) was added and the reactions contents were stirred vigorously at 25 °C for 5 min. Upon completion, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated to give the desired aldehyde **70** (1.21 g, quantitative yield assumed) as a yellow/orange foam which was carried forward without any additional purification. **70**: R_f = 0.59 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3001, 2938, 2838, 1694, 1608, 1588, 1514, 1462, 1441, 1429, 1393, 1344, 1295, 1249, 1204, 1176, 1156, 1137, 1065, 1034, 988, 829, 752, 692, 604, 538; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1 H), 7.23 (d, *J* = 8.6 Hz, 2 H), 6.96 (d, *J* = 2.3 Hz, 1 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 6.78 (d, *J* = 2.3 Hz, 1 H), 6.34 (t, *J* = 2.2 Hz, 1 H), 6.28 (d, *J* = 2.2 Hz, 2 H), 5.58 (d, *J* = 5.6 Hz, 1 H), 4.79 (d, *J* = 5.6 Hz, 1 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 3.73 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 162.4, 161.6, 161.4, 159.9, 146.0, 133.2, 133.2, 127.0, 124.0, 114.3, 106.6, 105.9, 102.3, 98.9, 94.0, 56.1, 56.0, 55.5 (3 C); HRMS (FAB+) calcd for $C_{25}H_{24}O_6^+$ [M^+] 420.1573, found 420.1580. Next, to the so-obtained crude aldehyde **70** (1.21 g, 2.89 mmol, 1.0 equiv) was added

THF (15 mL), *t*-BuOH (15 mL), and 2-methyl-2-butene (6.12 mL, 57.8 mmol, 20 equiv) at 25 °C under an ambient atmosphere. A solution of NaH_2PO_4 (3.61 g, 23.1 mmol, 8.0 equiv) in water (7 mL) and a solution of $NaClO_2$ (0.784 g, 8.67 mmol, 3.0 equiv) in water (7 mL) were then added sequentially. After stirring the resultant mixture at 25 °C for 12 h, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (10 mL), poured into water (15 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated to give the desired carboxylic acid **73** (1.26 g, quantitative yield assumed) as an orange foam which was carried forward without any additional purification. **73**: R_f = 0.38 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2938, 2838, 1694, 1609, 1594, 1514, 1491, 1462, 1342, 1293, 1249, 1203, 1175, 1156, 1127, 1066, 1037, 990, 931, 831, 736, 692, 538; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.7 Hz, 2 H), 7.12 (d, *J* = 2.4 Hz, 1 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 6.77 (d, *J* = 2.3 Hz, 1 H), 6.30 (t, *J* = 2.2 Hz, 1 H), 6.23 (d, *J* = 2.2 Hz, 2 H), 5.53 (d, *J* = 3.7 Hz, 1 H), 4.81 (d, *J* = 3.7 Hz, 1 H), 3.85 (s, 3 H), 3.79 (s, 3 H), 3.70 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 162.2, 161.0 (3 C), 159.7, 146.7, 134.0, 127.1, 126.8, 124.3, 114.3, 108.5, 105.7, 101.6, 98.6, 93.2, 57.1, 55.9, 55.4, 55.4; HRMS (FAB+) calcd for $C_{25}H_{24}O_7^+$ [M^+] 436.1522, found 436.1522. Finally, to a solution of the so-obtained crude carboxylic acid **73** (1.26 g, 2.89 mmol, 1.0 equiv) in acetone (40 mL) at 25 °C was sequentially added bromide **74** (1.423 g, 3.10 mmol, 1.1 equiv), K_2CO_3 (1.16 g, 8.40 mmol, 3.0 equiv), and *n*-Bu_4NI (0.103 g, 0.29 mmol, 0.1 equiv). The resultant reaction mixture was heated to 56 °C and stirred for 2 h. Upon completion, the reaction contents were quenched by the addition of water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc,

11:3→3:1) to give **75** (2.01 g, 85% yield from **60**) as a white foam. **75**: R_f = 0.69 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2935, 2838, 1720, 1592, 1514, 1455, 1431, 1371, 1328, 1285, 1248, 1203, 1159, 1123, 1066, 1027, 830, 778, 738, 697, 536; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.30 (m, 10 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 7.18 (d, *J* = 2.3 Hz, 1 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.75 (d, *J* = 2.3 Hz, 1 H), 6.54 (d, *J* =2.7 Hz, 1 H), 6.49 (d, *J* = 2.7 Hz, 1 H), 6.26 (t, *J* = 2.6 Hz, 1 H), 6.13 (d, *J* = 2.6 Hz, 2 H), 5.47 (d, *J* = 4.5 Hz, 1 H), 5.24 (d, *J* = 13.2 Hz, 1 H), 5.09 (s, 2 H), 5.03 (d, *J* = 13.2 Hz, 1 H), 4.90 (d, *J* = 11.5 Hz, 1 H), 4.88 (d, *J* = 4.4 Hz, 1 H), 4.86 (d, *J* = 11.4 Hz, 1 H), 3.87 (s, 3 H), 3.76 (s, 3 H), 3.63 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 162.3, 161.0, 161.0, 159.7, 158.8, 155.9, 146.5, 137.1, 136.5, 136.5, 133.7, 128.8, 128.7, 128.3, 128.1, 127.7, 127.1, 127.1, 123.1, 114.3, 108.3, 107.4, 105.4, 104.7, 102.0, 101.0, 98.6, 93.2, 71.0, 70.4, 66.3, 57.2, 55.9, 55.4, 55.3; HRMS (FAB+) calcd for $C_{46}H_{41}O_9Br^+$ [M^+] 816.1934, found 816.1957.

Ketone 71. *n*-BuLi (0.46 mL, 1.6 M in THF, 0.742 mmol, 1.5 equiv) was added slowly over the course of 5 min to a solution of **50** (0.300 g, 0.742 mmol, 1.5 equiv) in THF (10 mL) at –78 °C. After stirring the resultant solution at –78 °C for 20 min, a solution of **70** (0.208 g, 0.495 mmol, 1.0 equiv) in THF (5 mL) was added slowly at –78 °C via cannula, and the resultant mixture was stirred at –78 °C for 1 h. The reaction contents were then warmed slowly to 25 °C, and stirred for an additional 8 h. Upon completion, the reaction contents were quenched with saturated aqueous NH_4Cl (5 mL), poured into water (5 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to give the desired alcohol (0.228 g, 62% yield) as a yellow oil. Pressing forward, to a solution of this newly synthesized alcohol (0.130 g, 0.175 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 25 °C was

sequentially added $NaHCO_3$ (0.147 g, 1.75 mmol, 10.0 equiv) and Dess–Martin periodinane (0.104 g, 0.224 mmol, 1.2 equiv), and the resultant mixture was stirred at 25 °C for 30 min in an ambient atmosphere. Upon completion, saturated aqueous Na_2SO_3 (5 mL) was added and the reaction contents were stirred vigorously at 25 °C for 5 min. Upon completion, the reaction mixture was then poured into water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to give **71** (0.130 g, 99% crude yield) as a yellow oil. **71**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 6.86 (s, 1 H), 6.69 (d, *J* = 2.0 Hz, 1 H), 6.66 (s, 1 H), 6.26 (t, *J* = 2.0 Hz, 1 H), 6.11 (s, 2 H), 5.43 (d, *J* = 4.8 Hz, 1 H), 4.69 (d, *J* =14.8 Hz, 1 H), 4.21 (br s, 1 H), 3.81 (s, 3 H), 3.81 (s, 3 H), 3.80 (d, *J* =4.8 Hz, 1 H), 3.77 (s, 3 H), 3.43 (s, 3 H), 1.02 (m, 21 H).

Ketone 76. To a solution of **75** (2.01 g, 2.45 mmol, 1.0 equiv) in THF (100 mL) at –94 °C was added *n*-BuLi (1.84 mL, 1.6 M in hexanes, 2.94 mmol, 1.2 equiv) dropwise over the course of 15 min. The reaction mixture was then stirred at –94 °C for an additional 20 min, with TLC indicating the presence of residual starting material. Additional *n*-BuLi (0.46 mL, 1.6 M in hexanes, 0.74 mmol, 0.3 equiv) was then added dropwise in 3 equal portions at 20 min intervals until the consumption of **75** was verified by TLC analysis. Next, the cold bath was removed and the reaction contents were allowed to warm for 30 min, at which point TBDPSCl (1.92 mL, 7.37 mmol, 3.0 equiv) and DBU (0.37 mL, 2.45 mmol, 1.0 equiv) were added sequentially. The reaction mixture was then warmed to 50 °C and stirred for 12 h. Upon completion, the reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), poured into water (30 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with brine (50 mL), dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography

(silica gel, hexanes/EtOAc, 22:3→4:1) to give **76** (1.99 g, 83% yield) as a yellow foam. **76**: R_f = 0.72 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3053, 2957, 2933, 2859, 1735, 1656, 1597, 1514, 1462, 1429, 1373, 1316, 1265, 1248, 1204, 1175, 1154, 1130, 1113, 1058, 1045, 999, 942, 896, 831, 782, 733, 701, 608, 533, 504, 404; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.54 (m, 4 H), 7.39–7.29 (m, 11 H), 7.21–7.18 (m, 3 H), 7.11 (d, *J* = 7.6 Hz, 2 H), 6.91 (br s, 1 H), 6.84 (d, *J* = 3.9 Hz, 2 H), 6.75 (d, *J* = 8.5 Hz, 2 H), 6.73 (br s, 1 H), 6.69 (d, *J* = 2.3 Hz, 1 H), 6.32 (d, *J* = 1.8 Hz, 1 H), 6.20 (br s, 1 H), 6.01 (br s, 2 H), 5.34 (s, 1 H), 5.02 (d, *J* = 11.8 Hz, 1 H), 4.98 (d, *J* = 11.7 Hz, 1 H), 4.75 (d, *J* = 12.4 Hz, 1 H), 4.69 (d, *J* = 14.2 Hz, 1 H), 4.65 (br s, 2 H), 4.26 (br s, 1 H), 3.77 (S, 3 H), 3.75 (s, 3 H), 3.55 (s, 6 H), 1.00 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3, 162.2, 161.4, 161.1, 160.8, 159.6, 158.1, 145.9, 137.8, 136.7, 136.6, 135.6, 135.6, 133.9, 133.6, 133.5, 129.7, 128.8, 128.4, 128.2, 127.8, 127.6, 127.0, 126.6, 121.0, 119.7, 114.1, 108.8, 105.6, 104.5, 99.9, 99.1, 98.8, 93.3, 70.1, 69.9, 63.3, 57.1, 55.8, 55.4, 55.2, 27.0, 19.4; HRMS (FAB+) calcd for $C_{62}H_{60}O_9Si^+$ [M^+] 976.4007, found 976.4015.

Aldehyde 77. To a suspension of trimethylsulfonium iodide (4.12 g, 20.2 mmol, 10.0 equiv) in THF (60 mL) at 0 °C was added *n*-BuLi (10.1 mL, 1.6 M in hexanes, 16.2 mmol, 8.0 equiv). After stirring the resulting opaque pale yellow solution at 0 °C for 3 min, a solution of **76** (1.98 g, 2.02 mmol, 1.0 equiv) in THF (30 mL) was added via cannula over the course of 5 min. The reaction mixture was then warmed to 25 °C and stirred for 1 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (20 mL), poured into water (20 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were then washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. Pressing forward without any further purification, the so-obtained crude epoxide was dissolved in benzene (50 mL) and ZnI_2 (1.29 g, 4.04 mmol, 2.0 equiv) was added as a single portion at 25 °C in an

ambient atmosphere. Upon completion (generally 10–15 min as judged by careful TLC analysis), the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL), poured into water (30 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated to give the desired aldehyde **77** (2.00 g, 2.02 mmol, quantitative yield assumed) as a pale yellow foam and a 1:1 mixture of diastereomers. This material was carried forward without any further purification. **77**: R_f = 0.72 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3068, 3032, 3000, 2955, 2857, 2838, 1725, 1604, 1593, 1514, 1459, 1429, 1371, 1324, 1299, 1249, 1202, 1175, 1148, 1112, 1056, 999, 828, 739, 701, 610, 505; ^{1}H NMR (400 MHz, $CDCl_3$, 1:1 ratio of diastereomers) δ 9.42 (s, 1 H), 9.25 (s, 1 H), 7.59 (d, *J* = 6.5 Hz, 2 H), 7.54 (d, *J* = 6.9 Hz, 2 H), 7.48–7.13 (m, 38 H), 6.94 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 2.3 Hz, 1 H), 6.78 (d, *J* = 8.6 Hz, 2 H), 6.78 (d, *J* = 2.3 Hz, 1 H), 6.52 (d, *J* = 2.3 Hz, 1 H), 6.50 (d, *J* = 2.2 Hz, 1 H), 6.48 (d, *J* = 2.3 Hz, 1 H), 6.42 (d, *J* = 2.1 Hz, 1 H), 6.39 (d, *J* = 2.2 Hz, 1 H), 6.24 (t, *J* = 2.1 Hz, 1 H), 6.14 (t, *J* = 2.1 Hz, 1 H), 6.05 (d, *J* = 2.1 Hz, 2 H), 5.93 (d, *J* = 2.1 Hz, 2 H), 5.81 (d, *J* = 2.1 Hz, 1 H), 5.41 (d, *J* = 7.2 Hz, 1 H), 5.38 (d, *J* = 7.2 Hz, 1 H), 4.97 (d, *J* = 14.5 Hz, 1 H), 4.96 (s, 2 H), 4.95 (s, 2 H), 4.92 (d, *J* = 13.2 Hz, 1 H), 4.88 (s, 2 H), 4.59 (d, *J* = 13.8 Hz, 1 H), 4.40 (d, *J* = 11.2 Hz, 1 H), 4.39 (d, *J* = 8.3 Hz, 1 H), 4.36 (s, 1 H), 4.29 (d, *J* = 4.0 Hz, 1 H), 4.28 (d, *J* = 13.6 Hz, 1 H), 4.22 (s, 1 H), 3.97 (d, *J* = 7.2 Hz, 1 H), 3.81 (s, 6 H), 3.67 (s, 3 H), 3.64 (s, 3 H), 3.60 (s, 6 H), 3.46 (s, 6 H), 1.03 (s, 9 H), 0.98 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, 1:1 ratio of diastereomers) δ 197.9, 197.7, 161.4, 161.2, 161.2, 161.1, 161.1, 160.8, 159.7, 159.6, 159.5, 159.3, 157.2, 156.7, 144.8, 143.6, 143.1, 142.3, 137.0, 137.0, 136.5, 136.3, 135.8, 135.7, 135.6, 135.4, 134.4, 133.6, 133.2, 133.1, 133.1, 133.0, 130.0, 129.9, 129.7, 128.7, 128.7, 128.6, 128.3, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 127.4, 127.3,

127.0, 121.2, 121.0, 117.2, 114.6, 114.1, 107.6, 106.2, 105.9, 105.0, 100.3, 100.2, 99.4, 99.0, 95.3, 94.7, 93.6, 93.3, 70.9, 70.7, 70.1, 63.5, 63.5, 57.3, 57.2, 55.5, 55.4, 55.4, 55.4, 55.1, 53.3, 52.9, 27.0, 26.9, 19.4, 19.4; HRMS (FAB+) calcd for $C_{63}H_{62}O_9Si^+$ [M^+] 990.4163, found 990.4149.

Alcohol 78. Next, this crude aldehyde **77** (2.00 g, 12.4 mmol, 1.0 equiv) was dissolved in THF (40 mL) and 4-benzyloxyphenylmagnesium bromide (3.0 mL, 1.0 M in THF, 3.0 mmol, 1.5 equiv) was added at 25 °C. After stirring at 25 °C for 10 min, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (15 mL), poured into water (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant crude material by flash column chromatography (silica gel, hexanes/EtOAc, 17:3→4:1) afforded benzylic alcohol **78** (2.34 g, 99% yield from **76**, a mixture of 4 diastereomers) as a yellow foam.

Alcohols 79 and 80. To a solution of **78** (2.27 g, 1.94 mmol, 1.0 equiv) in EtOAc (50 mL) at 25 °C was sequentially added 10% Pd/C (6.18 g, 5.81 mmol, 3.0 equiv Pd), $NaHCO_3$ (0.488 g, 5.81 mmol, 3 equiv), and MeOH (50 mL). H_2 gas was then bubbled through the reaction mixture for 30 min, after which time the reaction contents were stirred at 25 °C under a H_2 atmosphere (1 atm) for 11 h. Upon completion, the reaction mixture was filtered by vacuum filtration using filter paper (Whatman 1) and a Buchner funnel. The filtrate was concentrated, dissolved in CH_2Cl_2 (30 mL), and *p*-toluenesulfonic acid (0.368 g, 1.94 mmol, 1.0 equiv) was added. The resultant solution was then stirred at 25 °C in an ambient atmosphere for 30 min. Upon completion, the reaction contents were quenched by the slow, careful addition of saturated aqueous $NaHCO_3$ (10 mL), poured into water (10 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant

crude product was dissolved in acetone (30 mL) at 25 °C and K_2CO_3 (2.14 g, 15.5 mmol, 8.0 equiv) and MeI (0.60 mL, 9.68 mmol, 5.0 equiv) were added sequentially in an ambient atmosphere. The reaction flask was then warmed to 56 °C for stirred for 12 h. Upon completion, the reaction contents were quenched by the addition of water (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. Pressing forward, the resultant crude residue was dissolved in THF (30 mL) at 25 °C and treated with TBAF (3.87 mL, 1.0 M in THF, 3.87 mmol, 2.0 equiv). After stirring the resultant solution at 25 °C for 1 h, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (10 mL), poured into water (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), concentrated, and purified by flash column chromatrography (silica gel, hexanes/EtOAc, 4:1) to give **79** (0.323 g, 24% yield) as a pale yellow foam along with **80** (0.353 g, 26% yield) also as a pale yellow foam. [Note: Solid $NaHCO_3$ was used in the hydrogenation to buffer the relatively high acidity of the palladium catalyst used. The progress of this hydrogenation varied heavily with different bottles of palladium catalyst and needed to be reinvestigated with each new bottle.] **79**: R_f = 0.31 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3515, 3001, 2934, 2838, 1611, 1590, 1513, 1488, 1461, 1437, 1339, 1301, 1248, 1195, 1175, 1154, 1134, 1054, 1034, 977, 930, 829, 776, 758, 735, 695, 671, 618, 578, 536; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.6 Hz, 4 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 6.68 (d, *J* = 8.6 Hz, 2 H), 6.52 (d, *J* = 1.9 Hz, 1 H), 6.48 (d, *J* = 2.0 Hz, 1 H), 6.37 (d, *J* = 2.2 Hz, 1 H), 6.28 (t, *J* = 2.1 Hz, 1 H), 6.21 (d, *J* = 2.0 Hz, 1 H), 5.96 (d, *J* = 2.0 Hz, 2 H), 5.36 (d, *J* = 4.7 Hz, 1 H), 5.20 (d, *J* = 8.4 Hz, 1 H), 4.25 (d, *J* = 8.6 Hz, 1 H), 3.98 (d, *J* = 13.6 Hz, 1 H), 3.85 (d, *J* = 13.6 Hz, 1 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.69 (s, 6 H), 3.49 (d, *J* = 4.7 Hz, 1 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 161.8, 161.6, 161.5, 161.3, 159.9, 159.6, 145.6, 140.1, 138.9, 134.0, 132.5, 127.7, 126.6, 120.9, 117.9, 114.1, 114.1, 105.9, 105.6, 99.0, 95.4, 94.8, 93.8, 92.8, 62.2, 56.3, 55.7, 55.5, 55.4, 55.3, 52.8; HRMS (FAB+) calcd for $C_{41}H_{40}O_9^+$ [M^+] 676.2672, found 676.2689. **80**: R_f = 0.34 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3512, 3000, 2937, 2838, 1612, 1594, 1513, 1491, 1462, 1438, 1342, 1303, 1248, 1203, 1194, 1176, 1156, 1132, 1057, 1035, 987, 829, 784, 757, 693, 613, 576, 539, 420; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 6.62 (br s, 2 H), 6.58 (br s, 2 H), 6.48 (br s, 1 H), 6.39 (br s, 2 H), 6.22 (br s, 1 H), 6.15 (t, *J* = 2.2 Hz, 1 H), 6.09 (br s, 2 H), 5.43 (br s, 1 H), 5.36 (d, *J* = 4.4 Hz, 1 H), 4.44 (br s, 1 H), 4.34 (d, *J* = 4.3 Hz, 1 H), 4.09 (s, 2 H), 3.80 (s, 3 H), 3.76 (s, 6 H), 3.75 (s, 3 H), 3.66 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 161.3, 161.2, 160.9, 159.7, 159.2, 146.5, 141.8, 137.8, 134.3, 133.1, 127.7, 126.7, 126.6, 120.9, 120.4, 114.2, 114.1, 113.8, 106.0, 105.4, 99.1, 95.5, 94.6, 93.0, 92.7, 62.9, 56.7, 55.6, 55.5, 55.2, 50.9; HRMS (FAB+) calcd for $C_{41}H_{40}O_{19}^+$ [M^+] 676.2672, found 676.2686.

Aldehyde 81. Dess–Martin periodinane (0.211 g, 0.50 mmol, 1.2 equiv) was added to a solution of **79** (0.280 g, 0.41 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) at 25 °C, and the resultant mixture was stirred for 30 min in an ambient atmosphere. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous Na_2SO_3 (5 mL) and stirred vigorously for 5 min at 25 °C. The reaction contents were then poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to give the desired aldehyde **81** (0.280 g, 99% yield) as a yellow foam which was carried on without further purification. **81**: R_f = 0.56 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3001, 2935, 2839, 1693, 1610, 1588, 1514, 1462, 1440, 1394, 1344, 1298, 1249,

1194, 1174, 1139, 1057, 1034, 977, 946, 930, 830, 763, 736, 696, 621, 599, 579, 537; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1 H), 7.07 (d, *J* = 8.7 Hz, 2 H), 7.05 (d, *J* = 8.7 Hz, 2 H), 6.91 (d, *J* = 2.3 Hz, 1 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 6.71 (d, *J* = 8.7 Hz, 2 H), 6.64 (d, *J* = 2.3 Hz, 1 H), 6.47 (d, *J* = 2.2 Hz, 1 H), 6.26 (t, *J* = 2.2 Hz, 1 H), 6.13 (d, *J* = 2.2 Hz, 1 H), 5.93 (d, *J* = 2.2 Hz, 2 H), 5.35 (d, *J* = 5.0 Hz, 1 H), 5.31 (d, *J* = 8.6 Hz, 1 H), 4.56 (d, *J* = 8.6 Hz, 1 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.69 (s, 6 H), 3.51 (d, *J* = 5.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 162.7, 162.2, 161.7, 161.4, 161.4, 161.1, 159.6, 145.1, 140.7, 133.9, 133.0, 131.7, 127.8, 126.7, 124.7, 120.4, 114.2, 114.1, 106.0, 105.7, 103.5, 102.6, 99.4, 94.9, 94.3, 92.9, 56.5, 56.0, 55.7, 55.5, 55.4, 55.4, 52.2; HRMS (FAB+) calcd for $C_{41}H_{38}O_9^+$ [M^+] 674.2516, found 674.2596.

Aldehyde 85. Dess–Martin periodinane (0.113 g, 0.27 mmol, 1.2 equiv) were added sequentially to a solution of **80** (0.150 g, 0.22 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) at 25 °C, and the resultant mixture was stirred for 30 min in an ambient atmosphere. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous Na_2SO_3 (5 mL) and stirred vigorously for 5 min at 25 °C. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated and to give **85** (0.150 g, >99% yield) as a yellow foam which was carried on without further purification. Rf = 0.58 (silica gel, hexanes/EtOAc, 3:2); **85**: IR (film) ν_{max} 3001, 2956, 2935, 2838, 1696, 1609, 1589, 1513, 1491, 1462, 1440, 1391, 1342, 1321, 1304, 1247, 1203, 1192, 1176, 1155, 1133, 1055, 1034, 989, 963, 950, 909, 827, 785, 729, 693, 646, 607, 575, 540; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (S, 1 H), 7.28 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 6.81 (br s, 1 H), 6.68 (s, 1 H), 6.60 (br s, 4 H), 6.40 (s, 1 H), 6.15 (br s, 2 H), 6.10 (t, *J*

= 2.2 Hz, 1 H), 6.00 (br s, 1 H), 5.41 (br s, 1 H), 5.30 (br s, 1 H), 4.85 (br s, 1 H), 4.73 (d, *J* = 3.2 Hz, 1 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.76 (s, 3 H), 3.71 (s, 3 H), 3.64 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 161.9, 161.7, 161.5, 161.2, 159.8, 159.4, 147.0, 141.7, 133.9, 132.8, 127.4, 126.8, 123.5, 120.6, 114.3, 114.1, 113.8, 109.9, 106.2, 105.6, 101.9, 99.1, 94.2, 93.7, 93.2, 56.0, 55.9, 55.5, 55.4, 55.3, 55.2, 50.1; HRMS (FAB+) calcd for $C_{41}H_{38}O_9^+$ [M^+] 674.2516, found 674.2497.

Permethylated *E*- and *Z*-Miyabenol C 86 and 87. KOt-Bu (0.25 mL, 1.0 M in THF, 0.25 mmol, 5.1 equiv) was added dropwise over the course of 5 min to a solution of phosphonate **82** (57.5 mg, 0.22 mmol, 5.0 equiv) in THF (1.5 mL) at –78 °C. After 20 min of stirring at –78 °C, a solution of aldehyde **85** (30.0 mg, 0.045 mmol, 1.0 equiv) in THF (1 mL) was added at –78 °C. The resultant solution was allowed to warm to 25 °C over the course of 1 h. Upon completion, the reaction mixture was quenched with saturated aqueous NH4Cl (2 mL), poured into water (2 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were then washed with brine (5 mL), dried (MgSO4), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc 85:15→4:1) to give permethylated miyabenol C **86** and **87** (31.0 mg, 89% yield, 1.2 : 1 separable mixture of *E*- to *Z*- respectively) each as pale yellow foams. **86**: R_f = 0.25 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3001, 2928, 2838, 1721, 1608, 1593, 1511, 1488, 1462, 1431, 1344, 1302, 1248, 1192, 1174, 1156, 1129, 1033, 989, 965, 830, 756, 693, 532, 451, 496; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.26 (d, *J* = 8.6 Hz, 2 H), 7.03 (d, *J* = 8.7 Hz, 2 H), 6.79 (d, *J* = 8.8 Hz, 2 H), 6.59 (d, *J* = 8.9 Hz, 2 H), 6.58 (d, *J* = 8.9 Hz, 2 H), 6.45 (d, *J* = 2.3 Hz, 1 H), 6.45 (d, *J* = 2.8 Hz, 1 H), 6.38 (d, *J* = 8.6 Hz, 2 H), 6.25 (t, *J* = 2.3 Hz, 1 H), 6.21 (s, 1 H), 6.11 (d, *J* = 2.2 Hz, 1 H), 5.90

(d, J = 12.2 Hz, 1 H), 5.81 (d, J = 2.2 Hz, 2 H), 5.67 (d, J = 12.3 Hz, 1 H), 5.37 (d, J = 3.1 Hz, 1 H), 5.21 (d, J = 3.1 Hz, 1 H), 4.16 (d, J = 3.1 Hz, 1 H), 3.85 (s, 3 H), 3.84 (d, J = 3.1 Hz, 1 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.73 (S, 3 H), 3.73 (s, 3 H), 3.57 (s, 6 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.0, 162.4, 162.2, 162.0, 161.9, 160.7, 160.0, 159.8, 148.0, 143.5, 139.1, 137.3, 135.8, 134.5, 130.9, 130.8, 129.8, 127.3, 127.0, 126.3, 121.2, 114.8, 114.5, 114.3, 107.0, 106.4, 105.9, 99.7, 95.3, 94.2, 93.4, 92.7, 57.1, 55.8, 55.7, 55.7, 55.5, 55.4, 55.3, 52.7; HRMS (FAB+) calcd for $C_{49}H_{46}O_9^+$ [M^+] 778.3142, found 778.3158. **87**: R_f= 0.28 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3000, 2936, 2837, 2029, 1703, 1604, 1590, 1512, 1462, 1433, 1351, 1303, 1248, 1203, 1192, 1174, 1157, 1131, 1057, 1033, 990, 963, 828, 778, 738, 693, 597, 575, 539, 410; (400 MHz, acetone-d_6) δ 7.22 (d, J = 8.7 Hz, 2 H), 7.20 (d, J = 8.8 Hz, 2 H), 7.01 (d, J = 15.7 Hz, 1 H), 6.84 (d, J = 8.7 Hz, 2 H), 6.74 (d, J = 8.7 Hz, 2 H), 6.70 (s, 1 H), 6.67 (d, J = 2.4 Hz, 5 H), 6.47 (d, J = 2.1 Hz, 1 H), 6.36 (s, 1 H), 6.23 (s, 2 H), 6.22 (d, J = 1.8 Hz, 1 H), 6.15 (s, 1 H), 5.47 (d, J = 4.9 Hz, 1 H), 5.19 (S, 1 H), 4.72 (s, 1 H), 4.52 (d, J = 2.6 Hz, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.72 (s, 3 H), 3.66 (s, 6 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 162.9, 162.4, 162.3, 161.9, 160.5, 160.5, 160.3, 147.1, 143.3, 135.8, 135.2, 134.5, 134.1, 131.1, 131.0, 130.6, 128.7, 127.7, 127.6, 123.7, 119.9, 115.1, 114.9, 114.3, 107.5, 106.4, 103.1, 99.6, 96.0, 94.5, 94.1, 92.7, 57.4, 55.8, 55.7, 55.6, 55.5, 55.5, 55.4, 50.8; HRMS (FAB+) calcd for $C_{49}H_{46}O_9^+$ [M^+] 778.3142, found 778.3164.

Carboxylic Acid 88a. To aldehyde **81** (6.0 mg, 0.009 mmol, 1.0 equiv) was added THF (0.5 mL), *t*-BuOH (0.5 mL), and 2-methyl-2-butene (0.05 mL, 0.472 mmol, 54 equiv) at 25 °C under an ambient atmosphere. A solution of NaH_2PO_4 (0.014 g, 0.090 mmol, 10.0 equiv) in water (0.5 mL) and a solution of $NaClO_2$ (3.0 mg, 0.033 mmol, 3.5 equiv) in water (0.5 mL) were then added sequentially. After stirring the resultant mixture at 25 °C for 12 h, the reaction

contents were quenched by the addition of saturated aqueous NH_4Cl (1 mL), and extracted with EtOAc (3 × 3 mL). The combined organic layers were then washed with brine (2 mL), dried ($MgSO_4$), filtered, and concentrated to give the desired carboxylic acid **88a** (6.0 mg, 99%) as an off-white foam. **88a**: IR (film) ν_{max} 3001, 2934, 2839, 1696, 1611, 1588, 1514, 1490, 1462, 1439, 1339, 1293, 1248, 1194, 1175, 1155, 1131, 1036, 986, 930, 830, 782, 756, 736, 693, 618, 581, 541 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.6 Hz, 2 H), 7.10 (d, *J* = 2.4 Hz, 1 H), 7.00 (d, *J* = 8.7 Hz, 2 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 6.69 (d, *J* = 8.7 Hz, 2 H), 6.60 (d, *J* = 2.0 Hz, 1 H), 6.43 (d, *J* = 2.2 Hz, 1 H), 6.27 (t, *J* = 2.2 Hz, 1 H), 5.92 (d, *J* = 2.2 Hz, 2 H), 5.85 (d, *J* = 2.2 Hz, 1 H), 5.37 (d, *J* = 4.6 Hz, 1 H), 5.18 (d, *J* = 5.9 Hz, 1 H), 4.69 (d, *J* = 5.9 Hz, 1 H), 3.83 (s, 3 H), 3.83 (s, 3 H), 3.76 (d, *J* = 5.2 Hz, 1 H), 3.75 (s, 3 H), 3.68 (s, 3 H), 3.66 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 162.5, 161.7, 161.6, 161.0, 160.8, 160.0, 159.6, 144.9, 142.3, 134.2, 133.1, 128.0, 127.7, 126.7, 121.8, 119.0, 114.2, 114.1, 108.2, 106.4, 105.3, 101.2, 98.7, 94.2, 93.0, 92.9, 56.6, 55.9, 55.5, 55.5, 55.4, 55.4, 53.3; HRMS (FAB+) calcd for $C_{41}H_{38}O_{10}^+$ [M^+] 690.2465, found 690.2494.

Carboxylic Acid 88b. To aldehyde **85** (4.0 mg, 0.006 mmol, 1.0 equiv) was added THF (0.5 mL), *t*-BuOH (0.5 mL), and 2-methyl-2-butene (0.1 mL, 0.944 mmol, 157 equiv) at 25 °C under an ambient atmosphere. A solution of NaH_2PO_4 (0.028 g, 0.179 mmol, 30.0 equiv) in water (0.5 mL) and a solution of $NaClO_2$ (6.0 mg, 0.060 mmol, 10 equiv) in water (0.5 mL) were then added sequentially. After stirring the resultant mixture at 25 °C for 12 h, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (1 mL), and extracted with EtOAc (3 × 3 mL). The combined organic layers were then washed with brine (2 mL), dried ($MgSO_4$), filtered, concentrated and purified by preparative TLC (hexanes/EtOAc, 3:2) to give the desired carboxylic acid **88b** (3.5 mg, 85%) as an off-white foam. **88b**: IR (film) ν_{max} 3001,

2930, 2840, 1713, 1611, 1591, 1513, 1491, 1433, 1356, 1305, 1247, 1193, 1174, 1156, 1128, 1059, 1035, 990, 929, 828, 784, 732, 693, 612, 578, 531, 481 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.7 Hz, 2 H), 7.04 (br s, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 6.68 (br s, 1 H), 6.59 (br d, *J* = 8.0 Hz, 2 H), 6.54 (br s, 2 H), 6.41 (d, *J* = 2.2 Hz, 1 H), 6.17 (br s, 2 H), 6.11 (t, *J* = 2.2 Hz, 1 H), 5.95 (br s, 1 H), 5.41 (br s, 1 H), 5.17 (br s, 1 H), 4.73 (d, *J* = 2.2 Hz, 1 H), 4.60 (br s, 1 H), 3.80 (s, 3 H), 3.75 (s, 6 H), 3.70 (s, 3 H), 3.64 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 161.7, 161.6, 161.2, 160.9 (2 C), 159.7, 159.3, 146.8, 142.1, 133.8, 132.9, 127.3, 127.0, 126.0, 125.8, 120.4, 114.1, 113.7, 108.7, 106.1, 105.8, 101.8, 98.8, 94.0, 93.6, 92.3, 56.4, 55.8, 55.5, 55.3, 55.2, 55.2, 50.6; HRMS (FAB+) calcd for $C_{41}H_{38}O_{10}^+$ [M^+] 690.2465, found 690.2494.

Alkyne 93. Ohira-Bestmann reagent (7.0 mg, 0.038 mmol, 2.0 equiv) was added to a solution of aldehyde **81** (12.5 mg, 0.019 mmol, 1.0 equiv) in MeOH/THF (2 mL, 3:1) followed by K_2CO_3 (10.5 mg, 0.076 mmol, 4.0 equiv) and the resultant mixture stirred for 12 h in an ambient atmosphere. Upon completion, the reaction mixture was quenched by the addition of water (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated to give **93** (12.5 mg, 99% yield) as a yellow oil which was carried forward without any further purification. **93**: R_f = 0.56 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3287, 30001, 2935, 2838, 2063, 1609, 1585, 1513, 1487, 1461, 1435, 1341, 1202, 1248, 1193, 1174, 1135, 1035, 977, 929, 828, 757, 736, 692, 648, 629, 538, 479 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.6 Hz, 2 H), 7.04 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 6.68 (d, *J* = 8.7 Hz, 2 H), 6.51 (d, *J* = 2.2 Hz, 1 H), 6.46 (d, *J* = 2.2 Hz, 1 H), 6.41 (d, *J* = 2.2 Hz, 1 H), 6.26 (d, *J* = 2.2 Hz, 1 H), 6.17 (d, *J* = 2.2 Hz, 1 H), 5.90 (d, *J* = 2.2 Hz, 2 H), 5.29 (d, *J* = 4.7 Hz, 1 H), 5.15 (d, *J* = 8.3 Hz, 1 H), 4.34 (d, *J* = 8.4 Hz, 1 H), 3.83 (s, 3 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 3.67 (s, 6 H), 3.51 (d, *J* = 4.8 Hz, 1 H), 2.84 (s, 1 H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 161.6, 161.6, 161.5, 161.0, 160.8, 159.9, 159.5, 145.2, 139.4, 134.2, 132.4, 128.0, 126.8, 123.4, 120.2, 119.8, 114.1, 114.0, 110.2, 106.6, 106.4, 98.4, 97.7, 94.6, 93.6, 92.9, 81.6, 80.9, 56.3, 55.8, 55.7, 55.5, 55.4, 55.3, 53.6; HRMS (FAB+) calcd for $C_{42}H_{38}O_8^+$ [M^+] 670.2567, found 670.2593.

Alkene 97. $AuCl_3$ (0.10 mL, 0.003 M in 1,2-dichloroethane, 0.30 mmol, 0.1 equiv) and AgOTf (0.10 mL, 0.009 M in 1,2-dichloroethane, 0.90 mmol, 0.3 equiv) were added sequentially to 1,2-dichloroethane (0.5 mL) and stirred at 25 °C until the initial yellow solution became colorless (generally 5–10 min). A solution of **93** (2.0 mg, 0.003 mmol, 1.0 equiv) in 1,2-dichloroethane (0.5 mL) was then added in a single portion and the reaction mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was filtered through a small silica gel plug eluting with EtOAc and concentrated directly to give **97** (2.0 mg, >90% yield) as a pale yellow oil. **97**: R_f = 0.56 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3000, 2927, 2837, 1597, 1511, 1490, 1460, 1431, 1326, 1301, 1248, 1201, 1175, 1157, 1132, 1102, 1053, 1034, 968, 909, 791, 765, 732, 693, 646, 572, 548, 521, 493, 481, 470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 12.3 Hz, 1 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 11.9 Hz, 1 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 6.55 (d, *J* = 8.8 Hz, 2 H), 6.51 (s, 1 H), 6.47 (d, *J* = 1.6 Hz, 1 H), 6.43 (d, *J* = 2.0 Hz, 1 H), 6.42 (t, *J* = 2.2 Hz, 1 H), 6.35 (d, *J* = 8.8 Hz, 2 H), 6.35 (d, *J* = 3.1 Hz, 2 H), 6.34 (d, *J* = 2.3 Hz, 1 H), 5.46 (d, *J* = 2.1 Hz, 1 H), 4.95 (d, *J* = 2.2 Hz, 1 H), 3.87 (s, 3 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.75 (d, *J* = 1.9 Hz, 1 H), 3.74 (s, 6 H), 3.67 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 162.2, 160.9, 159.8, 159.0, 158.3, 147.8, 138.7, 135.1, 134.0, 133.7, 128.2, 127.5, 127.0, 125.9, 121.1, 117.6, 114.4, 113.7, 113.7, 105.8, 102.5, 98.9, 96.2, 92.1, 92.0, 84.2, 56.6, 56.0, 55.8, 55.7, 55.5, 55.3, 52.9; HRMS (FAB+) calcd for $C_{42}H_{38}O_8^+$ [M^+] 670.2567, found 670.2567.

Ester 104. To a solution of carboxylic acid **73** (0.984 g, 2.26 mmol, 1.0 equiv) in acetone (40 mL) at 25 °C was sequentially added bromide **103** (0.918 g, 2.48 mmol, 1.1 equiv), K_2CO_3 (1.56 g, 11.28 mmol, 5.0 equiv), and *n*-Bu_4NI (85.0 mg, 0.23 mmol, 0.1 equiv). The resultant reaction mixture was heated to 56 °C and stirred for 2 h. Upon completion, the reaction contents were quenched by the addition of water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 17:3→3:1) to give ester **104** (1.56 g, 96% yield) as a white foam. **104**: R_f = 0.45 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2929, 2838, 1721, 1609, 1588, 1514, 1461, 1397, 1373, 1345, 1320, 1247, 1203, 1149, 1123, 1087, 1058, 1039, 1017, 925, 831, 778, 737, 691, 582; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2 H), 7.17 (d, *J* = 2.3 Hz, 1 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 6.80 (d, *J* = 2.7 Hz, 1 H), 6.74 (d, *J* = 2.3 Hz, 1 H), 6.66 (d, *J* = 2.8 Hz, 1 H), 6.28 (t, *J* = 2.2 Hz, 1 H), 6.13 (d, *J* = 2.2 Hz, 2 H), 5.46 (d, *J* = 4.6 Hz, 1 H), 5.21 (s, 2 H), 5.20 (d, *J* = 13.3 Hz, 1 H), 5.07 (d, *J* = 6.9 Hz, 1 H), 5.04 (d, *J* = 6.8 Hz, 1 H), 4.96 (d, *J* = 13.4 Hz, 1 H), 4.87 (d, *J* = 4.6 Hz, 1 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.68 (s, 6 H), 3.50 (s, 3 H), 3.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 162.3, 161.0, 159.7, 154.7, 146.5, 137.2, 133.7, 128.1, 127.1, 123.2, 114.2, 110.4, 108.2, 105.8, 105.4, 104.8, 101.0, 98.6, 95.4, 94.7, 93.2, 66.3, 57.2, 56.6, 56.2, 55.9, 55.5, 55.3; HRMS (FAB+) calcd for $C_{36}H_{38}O_{11}Br^+$ [M^+] 725.1597, found 725.1598.

Ketone 105. To a solution of ester **104** (1.55 g, 2.16 mmol, 1.0 equiv) in THF (35 mL) at –78 °C was added *n*-BuLi (2.03 mL, 1.6 M in hexanes, 3.24 mmol, 1.5 equiv) dropwise over the course of 15 min. The reaction mixture was then stirred for an additional 20 min at –94 °C, with TLC indicating the presence of residual starting material. Additional *n*-BuLi (0.41 mL, 1.6 M in

hexanes, 0.65 mmol, 0.3 equiv) was then added dropwise in 3 equal portions at 20 min intervals until the consumption of **104** was verified by TLC analysis. Next, the cold bath was removed and the reaction contents were allowed to warm for 30 min, at which point TBDPSCl (2.25 mL, 8.65 mmol, 4.0 equiv) and DBU (0.33 mL, 2.16 mmol, 1.0 equiv) were added sequentially. The reaction mixture was then warmed to 50 °C and stirred for 12 h. Upon completion, the reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL), poured into water (15 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 17:3→4:1) to give **105** (1.73 g, 80% yield) as a yellow foam. **105**: R_f = 0.58 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2960, 2856, 1666, 1604, 1514, 1462, 1428, 1397, 1340, 1316, 1292, 1250, 1203, 1175, 1144, 1110, 1084, 1023, 926, 804, 733, 703, 649, 609, 504; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 6.2 Hz, 2 H), 7.57 (d, *J* = 6.3 Hz, 2 H), 7.56–7.28 (m, 6 H), 7.22 (d, *J* = 8.5 Hz, 2 H), 6.96 (s, 1 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 6.68 (d, *J* = 2.0 Hz, 1 H), 6.64 (S, 2 H), 6.25 (s, 1 H), 6.21 (s, 2 H), 5.49 (d, *J* = 4.4 Hz, 1 H), 5.16 (s, 2 H), 4.93 (br s, 1 H), 4.76 (d, *J* = 6.9 Hz, 1 H), 4.72 (d, *J* = 6.9 Hz, 1 H), 4.58 (d, *J* = 13.5 Hz, 1 H), 4.50 (br s, 1 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 3.68 (s, 6 H), 3.48 (s, 3 H), 3.10 (s, 3 H), 0.94 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.7, 162.1, 160.9, 160.8, 159.6, 156.2, 146.4, 142.6, 136.9, 135.6, 134.9, 134.0, 133.5, 133.4, 129.7, 129.7, 127.8, 127.1, 121.4, 121.3, 114.2, 110.5, 107.9, 106.1, 101.8, 99.6 98.2, 94.6, 94.1, 93.5, 63.3, 56.5, 56.3, 55.9, 55.8, 55.4, 55.3, 26.8, 19.3; HRMS (FAB+) calcd for $C_{52}H_{57}O_{11}Si^+$ [M^+] 885.3670, found 885.3677.

Aldehyde 106. To a suspension of trimethylsulfonium iodide (3.93 g, 19.2 mmol, 10.0 equiv) in THF (60 mL) at 0 °C was added *n*-BuLi (10.8 mL, 1.6 M in hexanes, 17.3 mmol, 8.0 equiv). After stirring the resulting opaque pale yellow solution at 0 °C for 3 min, a solution of

105 (1.70 g, 1.92 mmol, 1.0 equiv) in THF (30 mL) was added via cannula over the course of 5 min. The reaction mixture was then warmed to 25 °C and stirred for 1 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (20 mL), poured into water (20 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were then washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. Pressing forward without any further purification, the so-obtained crude epoxide was taken up in benzene (50 mL) and ZnI_2 (1.26 g, 3.84 mmol, 2.0 equiv) was added as a single portion at 25 °C in an ambient atmosphere. Upon completion (generally 10–15 min as judged by careful TLC analysis), the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL), poured into water (30 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated to give **106** (1.72 g, 1.92 mmol, quantitative yield assumed) as a pale yellow foam. This material was a 1:1 mixture of diastereomers and was carried forward without any further purification. **106**: R_f = 0.58, 0.52 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2933, 2856, 1726, 1605, 1588, 1514, 1462, 1429, 1295, 1249, 1204, 1174, 1153, 1139, 1112, 1066, 1029, 924, 826, 736, 703, 610, 504, 491; ^{1}H NMR (400 MHz, $CDCl_3$, 1:1 ratio of diastereomers) δ 9.38 (s, 1 H), 9.21 (s, 1 H), 7.69 (d, *J* = 6.5 Hz, 2 H), 7.55 (d, *J* = 6.8 Hz, 2 H), 7.46 (d, *J* = 7.0 Hz, 4 H), 7.42–7.25 (m, 10 H), 7.22–7.16 (m, 4 H), 7.00 (d, *J* = 2.4 Hz, 1 H), 6.99 (d, *J* = 2.4 Hz, 1 H), 6.93 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 6.79 (d, *J* = 8.8 Hz, 2 H), 6.78 (s, 2 H), 6.47 (d, *J* = 2.2 Hz, 1 H), 6.42 (d, *J* = 2.2 Hz, 1 H), 6.31 (d, *J* = 2.2 Hz, 1 H), 6.25 (t, *J* = 2.2 Hz, 1 H), 6.14 (t, *J* = 2.2 Hz, 1 H), 6.02 (d, *J* = 2.2 Hz, 2 H), 5.96 (d, *J* = 2.2 Hz, 2 H), 5.76 (d, *J* = 2.0 Hz, 1 H), 5.42 (d, *J* = 7.5 Hz, 1 H), 5.40 (d, *J* = 7.9 Hz, 1 H), 5.12 (d, *J* = 6.6 Hz, 1 H), 5.11 (s, 2 H), 5.10 (d, *J* = 6.5 Hz, 1 H), 5.06 (d, *J* = 6.8 Hz, 1 H), 5.01 (d, *J* = 6.8 Hz, 1 H), 4.99 (d, *J* = 8.4 Hz, 1 H), 4.96 (d, *J* = 6.8 Hz, 1 H), 4.59

(d, J = 13.5 Hz, 1 H), 4.41 (d, J = 11.7 Hz, 1 H), 4.38 (d, J = 7.9 Hz, 1 H), 4.33 (d, J = 13.7 Hz, 1 H), 4.24 (d, J = 13.5 Hz, 1 H), 4.23 (s, 1 H), 4.17 (s, 1 H), 4.00 (d, J = 7.4 Hz, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.72 (s, 3 H), 3.63 (s, 3 H), 3.62 (s, 6 H), 3.47 (s, 6 H), 3.46 (s, 3 H), 3.46 (s, 3 H), 3.40 (s, 3 H), 3.30 (s, 3 H), 1.03 (s, 9 H), 0.97 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 197.0, 161.4, 161.2, 161.1, 161.1, 161.0, 159.7, 159.7, 158.1, 157.8, 156.0, 155.3, 144.7, 143.3, 143.2, 142.0, 135.8, 135.7, 135.7, 135.5, 135.4, 133.9, 133.6, 133.1, 133.0, 133.0, 130.0, 129.9, 129.7, 128.5, 127.9, 127.9, 127.8, 127.7, 127.6, 127.1, 121.3, 121.2, 118.2, 115.0, 114.2, 114.1, 109.0, 108.2, 107.7, 106.4, 106.3, 102.3, 102.2, 99.4, 99.0, 95.0, 94.8, 94.6, 94.6, 94.6, 94.5, 93.7, 93.4, 63.3, 57.5, 57.3, 56.6, 56.4, 56.2, 56.1, 55.5, 55.4, 55.4, 55.1, 53.0, 26.9, 26.8, 19.4 (2 C); HRMS (FAB+) calcd for $C_{53}H_{58}O_{11}Si^+$ [M^+] 898.3748, found 898.3744.

Ketone 107. To a solution of crude aldehyde **106** (1.72 g, 1.63 mmol, 1.0 equiv) in THF (40 mL) at 25 °C was added 4-methoxyphenylmagnesium bromide (2.45 mL, 1.0 M in THF, 2.45 mmol, 1.5 equiv) and the reaction mixture was allowed to stir for 10 min at 25 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (10 mL), poured into water (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with brine (30 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1→4:1) to give the desired benzylic alcohol (1.58 g, 82% yield from **105**) as a mixture of 4 diastereomers. This mixture of benzylic alcohols was then dissolved in CH_2Cl_2 (30 mL) at 25 °C and $NaHCO_3$ (1.32 g, 15.7 mmol, 10.0 equiv) and Dess–Martin periodinane (0.800 g, 1.88 mmol, 1.2 equiv) were added sequentially in single portions in an ambient atmosphere. After stirring the resultant slurry at 25 °C for 30 min, the reaction contents were quenched by the addition of Na_2CO_3 (10 mL), poured into saturated aqueous $NaHCO_3$ (20 mL), and extracted with EtOAc (3 × 30 mL). The combined

organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1→4:1) to give the desired benzylic ketone **107** (1.54 g, 98%) as a yellow foam and as a 1:1 mixture of diastereomers.

Alcohol 108. Benzylic ketone **107** (0.218 g, 0.22 mmol, 1.0 equiv) was dissolved in THF (10 mL) and concentrated HCl (1.8 mL, 12 M in water, 22 mmol, 100 equiv) was added at 25 °C in an ambient atmosphere. The reaction contents were then warmed to 40 °C and stirred for 4 h. Upon completion, the reaction contents were quenched by the slow, careful addition of saturated aqueous $NaHCO_3$ (5 mL), poured into water (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), concentrated, and carried forward without any additional purification. Next, this newly-obtained crude residue was dissolved in acetone (10 mL) at 25 °C and K_2CO_3 (0.300 g, 2.17 mmol, 10.0 equiv) and MeI (0.05 mL, 1.1 mmol, 5.0 equiv) were added sequentially. The reaction contents were then warmed to 56 °C and stirred for 2 h. Upon completion, the reaction contents were quenched by the addition of water (5 mL) and extracted by EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), concentrated. Pressing forward without any additional purification, the so-obtained crude residue was next dissolved in THF (5 mL) and TBAF (0.50 mL, 1.0 M in THF, 0.50 mmol, 2.3 equiv) was added at 25 °C. The reaction contents were then warmed to 50 °C and stirred for 12 h. Upon completion, the reaction mixture weas quenched by the addition of saturated aqueous NH_4Cl (3 mL), poured into water (3 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with brine (5 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) to give atropisomeric alcohols **108a** and **108b**

(77.0 mg, 53% yield from **107, 108a**:**108b** = 1:2). Warming either of the pure atropisomers in toluene at 80 °C for 12 h established a 2.5:1 ratio of these materials. **108a**: R_f = 0.39 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3507, 2938, 2836, 1609, 1511, 1461, 1426, 1372, 1343, 1304, 1246, 1194, 1177, 1137, 1066, 1033, 993, 976, 941, 790, 733, 692, 633, 608, 574, 550, 529, 489, 462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.8 Hz, 2 H), 7.10 (d, *J* = 8.8 Hz, 2 H), 6.94 (d, *J* = 1.6 Hz, 1 H), 6.85 (d, *J* = 8.0 Hz, 2 H), 6.84 (br s, 1 H), 6.71 (d, *J* = 1.6 Hz, 1 H), 6.63 (d, *J* = 8.8 Hz, 2 H), 6.52 (d, *J* = 2.0 Hz, 1 H), 5.83 (br s, 1 H), 5.76 (d, *J* = 1.6 Hz, 2 H), 5.72 (d, *J* = 5.2 Hz, 1 H), 4.30 (d, *J* = 13.2 Hz, 1 H), 4.15 (d, *J* = 13.2 Hz, 1 H), 3.93 (d, *J* = 5.2 Hz, 1 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.42 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 161.3, 160.4, 159.5, 159.1, 157.9, 154.5, 149.9, 144.2, 134.6, 134.1, 132.8, 126.9, 126.3, 123.0, 122.8, 120.8, 114.2, 113.3, 11.6, 110.5, 108.7, 105.3, 98.9, 96.6, 95.2, 92.7, 61.6, 57.5, 55.9, 55.8, 55.4, 55.3, 54.9; HRMS (FAB+) calcd for $C_{41}H_{38}O_9^+$ [M^+] 674.2516, found 674.2490 (mixture). **108b**: R_f = 0.32 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3506, 2998, 2931, 2835, 1608, 1595, 1511, 1492, 1460, 1425, 1380, 1321, 1305, 1249, 1194, 1177, 1138, 1066, 1031, 992, 943, 829, 693, 620, 595, 580, 527, 482 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.9 Hz, 2 H), 7.00 (d, *J* = 8.7 Hz, 2 H), 6.80 (s, 2 H), 6.80 (d, *J* = 9.1 Hz, 2 H), 6.74 (d, *J* = 8.7 Hz, 2 H), 6.60 (d, *J* = 2.2 Hz, 1 H), 6.55 (d, *J* = 2.2 Hz, 1 H), 5.88 (d, *J* = 2.2 Hz, 2 H), 5.84 (t, *J* = 2.2 Hz, 1 H), 5.59 (d, *J* = 6.4 Hz, 1 H), 4.23 (d, *J* = 9.5 Hz, 1 H), 4.09 (d, *J* = 9.9 Hz, 1 H), 3.84 (s, 3 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.79 (d, *J* = 6.5 Hz, 1 H), 3.76 (s, 3 H), 3.52 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 160.8, 160.3, 159.6, 159.5, 158.0, 154.4, 149.4, 144.6, 135.8, 133.3, 132.4, 127.3, 127.0, 124.1, 123.7, 120.4, 114.3, 114.0, 113.3, 109.3, 108.2, 106.2, 97.8, 96.4, 94.4, 92.6, 61.4, 56.5, 55.9, 55.8, 55.4, 55.3, 55.2; HRMS (FAB+) calcd for $C_{41}H_{38}O_9^+$ [M^+] 674.2516, found 674.2490 (mixture).

Alkyne 98. Dess–Martin periodinane (19.0 mg, 0.044 mmol, 1.2 equiv) was added to a solution of **108b** (25.0 mg, 0.037 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at 25 °C, and the resultant slurry was stirred at 25 °C for 30 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous Na_2SO_3 (2 mL), stirred vigorously for 5 min, poured into saturated aqueous $NaHCO_3$ (4 mL), and extracted with EtOAc (3 × 4 mL). The combined organic layers were then washed with brine (5 mL), dried ($MgSO_4$), and concentrated to give the desired aldehyde **109b** (25.0 mg, 99% yield) as a yellow oil. Pressing forward without any additional purification, the newly-synthesized aldehyde **109b** (2.0 mg, 0.003 mmol, 1.0 equiv) was dissolved in THF (0.5 mL) and MeOH (0.5 mL) at 25 °C and solid K_2CO_3 (5.0 mg, 0.036 mmol, 12.0 equiv) and the Ohira-Bestmann reagent (0.011 mL, 0.072 mmol, 24 equiv) were added sequentially. After stirring the resultant solution at 25 °C for 12 h, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL), poured into water (1 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), and concentrated to give **98** (2.0 mg, 99% yield, 2:1 atropisomer mixture favoring the one that corresponds to the atropisomerically pure starting aldehyde **108b,** i.e. **98b**) as a yellow oil. **98**: R_f = 0.50 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3296, 3054, 3003, 2931 2839, 1611, 1513, 1489, 1462, 1428, 1380, 1349, 1325, 1298, 1249, 1193, 1178, 1138, 1067, 1035, 973, 930, 876, 831, 792, 734, 103, 625, 564, 529 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (**98a**) δ 7.28 (d, *J* = 8.8 Hz, 2 H), 7.27 (d, *J* = 7.9 Hz, 2 H), 7.00 (d, *J* = 2.1 Hz, 1 H), 6.93 (d, *J* = 2.1 Hz, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 6.70 (d, *J* = 8.9 Hz, 2 H), 6.61 (d, *J* = 2.2 Hz, 1 H), 6.51 (d, *J* = 2.2 Hz, 1 H), 5.84 (t, *J* = 2.2 Hz, 1 H), 5.73 (br s, 2 H), 5.63 (d, *J* = 7.2 Hz, 1 H), 4.25 (d, *J* = 7.2 Hz, 1 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.79 (s, 3 H), 3.34 (s, 6 H), 2.77 (s, 1 H); (**98b**) 7.46 (d, *J* = 8.8 Hz, 2 H), 7.03 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 2.2 Hz, 1 H), 6.82 (d, *J*

= 9.0 Hz, 2 H), 6.77 (br s, 1 H), 6.76 (d, *J* = 8.5 Hz, 2 H), 6.68 (d, *J* =2.2 Hz, 1 H), 6.57 (d, *J* = 2.2 Hz, 1 H), 5.86 (d, *J* = 2.1 Hz, 1 H), 5.83 (t, *J* = 2.1 Hz, 1 H), 5.50 (d, *J* = 7.5 Hz, 1 H), 3.86 (s, 3 H), 3.82 (s, 6 H), 3.77 (s, 3 H), 3.77 (d, *J* = 7.4 Hz, 1 H), 3.55 (s, 6 H), 2.84 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, atropisomer mixture) δ 161.0, 160.7, 160.6, 160.5, 160.2, 160.2, 159.7, 159.7, 159.5, 159.4, 157.2, 157.0, 154.3, 154.1, 150.5, 144.2, 143.7, 133.5, 133.2, 131.0, 130.4, 127.6, 127.4, 127.3, 127.3, 125.1, 124.3, 124.1, 123.6, 123.4, 123.0, 115.7, 115.6, 114.3, 114.1, 114.0, 114.0, 113.9, 113.9, 113.5, 112.6, 110.1, 109.2, 105.8, 105.6, 99.1, 98.7, 97.9, 97.4, 96.5, 96.2, 93.5, 92.9, 81.1, 81.0, 80.3, 80.1, 57.4, 57.1, 56.1, 55.9, 55.8, 55.4, 55.4, 55.3, 55.1, 54.9; HRMS (FAB+) calcd for $C_{42}H_{36}O_8^+$ [M^+] 668.2410, found 668.2388.

Exocyclic Olefin 99. $AuCl_3$ (0.10 mL, 0.003 M in 1,2-dichloroethane, 0.30 mmol, 0.1 equiv) and AgOTf (0.10 mL, 0.009 M in 1,2-dichloroethane, 0.90 mmol, 0.3 equiv) were added sequentially to 1,2-dichloroethane (0.5 mL) and stirred at 25 °C until the initial yellow color had disappeared (generally 5–10 min). A solution of **98** (2.0 mg, 0.003 mmol, 1:2 mixture of atropisomers **98a:98b** , 1.0 equiv) in 1,2-dichlorothane (0.5 mL) was then added in a single portion and the resultant reaction mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was filtered through Celite, concentrated, and purified by preparative TLC (CH_2Cl_2/*t*-BuOH, 19:1) to give **99** (1.3 mg, >90% yield based on the productive atropisomer **98b**) as a pale yellow oil along with the recovered unproductive atropisomer. **99**: R_f = 0.50 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2928, 2837, 1610, 1581, 1511, 1486, 1461, 1413, 1378, 1306, 1249, 1199, 1176, 1138, 1078, 1033, 987, 908, 875, 830, 644, 574, 550, 530, 490, 467 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.8 Hz, 2 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 6.93 (d, *J* = 2.0 Hz, 1 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 2.4 Hz, 1 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 6.46 (d, *J* = 2.4 Hz, 1 H), 6.29 (d, *J* = 2.4 Hz, 1 H), 6.14 (d, *J* = 2.4 Hz, 1 H), 5.98 (d, *J* =

2.4 Hz, 1 H), 5.58 (d, *J* = 6.0 Hz, 1 H), 5.13 (d, *J* = 1.6 Hz, 1 H), 5.02 (d, *J* = 1.6 Hz, 1 H), 4.77 (d, *J* = 6.0 Hz, 1 H), 3.83 (s, 3 H), 3.81 (s, 6 H), 3.80 (s, 3 H), 3.65 (s, 3 H), 3.55 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 161.1, 159.9, 159.4, 158.8, 158.0, 157.7, 154.1, 150.2, 139.8, 139.3, 138.4, 133.7, 133.3, 128.1, 127.8, 123.9, 123.5, 120.9, 120.7, 118.9, 115.2, 114.1, 114.0, 110.8, 109.0, 106.6, 97.7, 96.5, 95.2, 94.5, 56.7, 55.9, 55.8, 55.6, 55.5, 55.4, 55.1; HRMS (FAB+) calcd for $C_{42}H_{36}O_8^+$ [M^+] 668.2410, found 668.2421.

Allylic Alcohol 110. To a solution of aldehyde **109b** (8.0 mg, 0.012 mmol, 1.0 equiv) in THF (1 mL) at 25 °C was added vinylmagnesium bromide (0.05 mL, 1.0 M in THF, 0.05 mmol, 4.0 equiv) and the resulting mixture was stirred at 25 °C for 10 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (1 mL), poured into water (2 mL), and extracted with EtOAc (3 × 3 mL). The combined organic layers were then washed with brine (3 mL), dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:1) to give **110** (6.0 mg, 75% yield) as a pale yellow oil. **110**: R_f = 0.40 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3503, 2931, 2839, 1612, 1512, 1462, 1427, 1383, 1307, 1252, 1179, 1146, 1169, 1034, 989, 926, 832, 732 692, 530 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.9 Hz, 2 H), 7.01 (d, *J* = 8.7 Hz, 2 H), 6.85 (d, *J* = 2.3 Hz, 1 H), 6.81 (d, *J* = 8.9 Hz, 2 H), 6.77 (d, *J* = 2.2 Hz, 1 H), 6.75 (d, *J* = 8.7 Hz, 2 H), 6.58 (d, *J* = 2.2 Hz, 1 H), 6.54 (d, *J* = 2.2 Hz, 1 H), 5.95 (ddd, *J* = 17.1, 10.5, 4.8 Hz, 1 H), 5.94 (d, *J* = 2.1 Hz, 2 H), 5.79 (t, *J* = 1.9 Hz, 1 H), 5.55 (d, *J* = 7.8 Hz, 1 H), 5.09 (d, *J* = 10.5 Hz, 1 H), 5.05 (d, *J* = 17.2 Hz, 1 H), 4.97 (d, *J* = 3.8 Hz, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.79 (d, *J* = 7.6 Hz, 1 H), 3.76 (s, 3 H), 3.55 (s, 6 H), 2.86 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 160.9, 160.0, 159.6, 159.5, 158.1, 154.3, 149.6, 144.5, 139.9, 138.3, 132.9, 132.0, 127.4, 127.0, 124.0, 123.7, 120.4, 115.1, 114.3, 114.0, 113.3, 108.7, 108.6, 106.8, 97.1,

96.7, 94.7, 92.9, 68.9, 56.7, 55.9, 55.8, 55.4, 55.3, 55.3; HRMS (FAB+) calcd for $C_{43}H_{40}O_9^+$ [M^+] 700.2672, found 700.2673.

Alkene 111. Methanesulfonic acid (0.01 mL, 0.15 mmol, 50 equiv) was added to a solution of **110** (2.0 mg, 0.003 mmol, 1.0 equiv) in THF (1 mL) at 25 °C in an ambient atmosphere, and the resultant mixture was allowed to stir at 25 °C for 3 h. Upon completion, the reaction mixture was quenched carefully by the slow addition of saturated aqueous $NaHCO_3$ (1 mL), poured into water (1 mL), and extracted with EtOAc (3 × 3 mL). The combined organic layers were then washed with brine (2 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) to give **111** (1.6 mg, 80% yield) as a pale yellow oil. **111**: R_f = 0.45 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3000, 2931, 2838, 1611, 1511, 1486, 1463, 1416, 1381, 1343, 1305, 1250, 1197, 1177, 1143, 1071, 1035, 983, 831, 737, 634, 525 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.9 Hz, 2 H), 7.23 (d, *J* = 8.7 Hz, 2 H), 7.12 (d, *J* = 2.2 Hz, 1 H), 6.88–6.83 (m, 1 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 8.9 Hz, 2 H), 6.77 (d, *J* = 2.2 Hz, 1 H), 6.52 (d, *J* = 2.4 Hz, 1 H), 6.49 (d, *J* = 6.2 Hz, 1 H), 6.19 (d, *J* = 2.0 Hz, 1 H), 6.16 (d, *J* = 2.5 Hz, 1 H), 5.43 (d, *J* = 2.5 Hz, 1 H), 5.24 (d, *J* = 11.6 Hz, 1 H), 5.10 (dt, *J* = 10.2, 1.6 Hz, 1 H), 5.01 (dt, *J* = 17.2, 1.6 Hz, 1 H), 4.87 (d, *J* = 11.6 Hz, 1 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.70 (s, 3 H), 3.61 (s, 3 H), 3.28 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 160.5, 160.0, 159.7, 159.4, 157.9, 157.5, 154.3, 151.3, 139.0, 138.6, 136.0, 132.6, 131.0, 129.1, 128.3, 124.1, 123.5, 121.8, 121.2, 115.4, 115.1, 113.9, 113.8, 112.1, 110.5, 108.3, 99.6, 96.9, 93.9, 93.3, 60.3, 55.9, 55.6, 55.5, 55.4, 55.1, 54.8, 41.5; HRMS (FAB+) calcd for $C_{43}H_{38}O_8^+$ [M^+] 682.2567, found 682.2587.

Aldehyde 112. NMO (3.0 mg, 0.03 mmol, 10 equiv) and OsO_4 (0.001 mL, 2.5 wt % in *t*-BuOH, 0.001 mmol, 0.4 equiv) were added sequentially to a solution of **111** (1.6 mg, 0.0023

mmol, 1 equiv) in acetone (0.5 mL) and water (0.1 mL) at 25 °C in an ambient atmosphere. The reaction flask was sealed to prevent solvent evaporation and the contents were stirred at 25 °C for 12 h. Upon completion, the reaction mixture was quenched with saturated aqueous Na_2SO_3 (1 mL), poured into water (1 mL), and extracted with EtOAc (3 × 3 mL). The combined organic layers were then washed with brine (2 mL), dried ($MgSO_4$), filtered, and concentrated. Pressing forward without any additional purification, $NaIO_4$ on silica (10 mg, 0.7 mmol/g, 0.007 mmol, 3.0 equiv) was added to a solution of the so-obtained crude diol in CH_2Cl_2 (0.5 mL) at 25 °C in an ambient atmosphere. After stirring the resultant slurry for 20 min at 25 °C, the mixture was filtered through a pad of Celite, concentrated, and purified by preparative TLC (hexanes/EtOAc, 1:1) to give aldehyde **112** (1.2 mg, 75%) as a pale yellow oil. **112**: R_f = 0.42 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2998, 2932, 2836, 1722, 1607, 1510, 1486, 1461, 1420, 1379, 1343, 1320, 1305, 1249, 1202, 1176, 1141, 1085, 1068, 1031, 982, 735, 701, 636, 527, 471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1 H), 7.50 (d, *J* = 8.8 Hz, 2 H), 7.28 (d, *J* = 8.8 Hz, 2 H), 7.11 (d, *J* = 2.0 Hz, 1 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 6.84 (d, *J* = 9.2 Hz, 2 H), 6.84 (d, *J* = 2.4 Hz, 1 H), 6.52 (d, *J* = 2.4 Hz, 1 H), 6.23 (d, *J* = 2.4 Hz, 2 H), 6.14 (S, 1 H), 5.68 (d, *J* = 2.4 Hz, 1 H), 5.34 (d, *J* = 9.6 Hz, 1 H), 4.95 (d, *J* = 9.2 Hz, 1 H), 3.82 (s, 3 H), 3.82 (s, 3 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 3.64 (s, 3 H), 3.39 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 161.8, 161.5, 160.2, 159.6, 159.0, 158.3, 157.8, 154.5, 151.0, 139.5, 133.3, 131.9, 128.9, 128.1, 123.3, 121.6, 119.8, 119.6, 114.6, 114.1, 114.1, 111.5, 111.2, 108.1, 98.7, 97.2, 94.7, 94.3, 58.4, 55.8, 55.7, 55.5, 55.5, 55.4, 55.0, 49.0; HRMS (FAB+) calcd for $C_{42}H_{36}O_9^+$ [M^+] 684.2359, found 684.2341.

Bromide S2. To a solution of 3,5-dibenzyloxybenzyl alcohol **113** (13.9 g, 43.4 mmol, 1.0 equiv) in CH_2Cl_2 (250 mL) at 0 °C was added solid NBS (3.86 g, 21.7 mmol, 0.5 equiv) in

multiple portions over 10 min. After stirring the resultant solution for 30 min at 0 °C, a second portion of NBS was added (3.86 g, 21.7 mmol, 0.5 equiv) and the reaction was stirred for an additional 30 min at 0 °C. The cold bath was then removed and the reaction mixture allowed to warm to 25 °C over 12 h. The reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (100 mL), poured into water (50 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were then washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to give the desired halogenated intermediate **S2** (17.3 g, 99% yield) as a white solid that was carried forward without additional purification. **S2**: R_f = 0.44 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3373, 3065, 3033, 2923, 1587, 1498, 1446, 1376, 1325, 1280, 1216, 1161, 1063, 1022, 909, 833, 736, 697, 467 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.32 (m, 10 H), 6.81 (d, *J* = 2.4 Hz, 1 H), 6.56 (d, *J* = 2.8 Hz, 1 H), 5.11 (s, 2 H), 5.04 (s, 2 H), 4.75 (d, *J* = 4.0 Hz, 2 H), 2.00 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 155.9, 142.0, 136.7, 136.5, 128.8, 128.7, 128.3, 128.1, 127.7, 127.2, 106.6, 103.5, 101.5, 71.1, 70.5, 65.5; HRMS (FAB+) calcd for $C_{21}H_{19}BrO_3^+$ [M^+] 398.0518, found 398.9532.

Ester 114. Bromide **S2** (17.3 g, 43.4 mmol, 1.0 equiv), 3.5-dibenzyloxybenzoic acid (14.5 g, 43.4 mmol, 1.0 equiv), and Ph_3P (12.5 g, 47.7 mmol, 1.05 equiv) were dissolved THF (400 mL), cooled to 0 °C, and then DIAD (9.4 mL, 47.7 mmol, 1.05 equiv) was then added dropwise over the course of 10 min. The reaction mixture was then allowed to warm to 25 °C over 15 min after which time it was concentrated directly and eluted through a short flash chromatography column (silica gel, hexanes/EtOAc, 9:1). The crude product was then recrystallized from CH_2Cl_2/hexanes (1:20) to give **114** (28.3 g, 91% yield) as a white solid. **114**: R_f = 0.63 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3033, 1718, 1593, 1497, 1444, 1374, 1326, 1297, 1223, 1161, 1056, 1027, 837, 736, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–

7.34 (m, 22 H), 6.82 (t, J = 2.4 Hz, 1 H), 6.74 (d, J = 2.8 Hz, 1 H), 6.60 (d, J = 2.8 Hz, 1 H), 5.42 (s, 2 H), 5.13 (s, 2 H), 5.08 (s, 4 H), 5.01 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 160.0, 158.9, 156.1, 137.4, 136.6, 136.5, 136.4, 132.0, 128.8, 128.8, 128.8, 128.3, 128.3, 128.1, 127.8, 127.7, 127.2, 108.8, 107.8, 107.5, 104.7, 101.9, 71.2, 70.5, 70.5, 66.7; HRMS (FAB+) calcd for $C_{42}H_{35}BrO_6^+$ [M^+] 714.1617, found 714.1630.

Ketone 115. To a solution of ester **114** (10.1 g, 14.1 mmol, 1.0 equiv) in THF (500 mL) at –105 °C was added *n*-BuLi (10.6 mL, 1.6 M in hexanes, 16.9 mmol, 1.2 equiv) dropwise over the course of 15 min. The reaction mixture was then stirred for an additional 20 min at –105 °C, with TLC indicating the presence of residual starting material. Additional *n*-BuLi (3.00 mL, 1.6 M in hexanes, 4.8 mmol, 0.34 equiv) was then added dropwise in 3 equal portions at 20 min intervals until the consumption of **114** was verified by TLC analysis. Next, the cold bath was removed and the reaction contents were allowed to warm for 30 min, at which point TBDPSCl (7.40 mL, 28.2 mmol, 2.0 equiv) and DBU (1.05 mL, 7.02 mmol, 0.5 equiv) were added sequentially. The reaction mixture was then warmed to 50 °C and stirred for an additional 12 h, after which time it was quenched by the addition of saturated aqueous NH_4Cl (150 mL), poured into water (100 mL), and extracted with EtOAc (3 × 150 mL). The combined organic layers were then washed with brine (150 mL), dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 19:1→9:1) to give **115** (10.2 g, 83% yield) as a pale yellow oil. **115**: R_f = 0.63 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3068, 3033, 2931, 2858, 1667, 1592, 1497, 1454, 1440, 1375, 1319, 1294, 1216, 1154, 1112, 1055, 1030, 998, 909, 843, 822, 737, 698, 607, 504 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 1.4 Hz, 8.0 Hz, 4 H), 7.46–7.30 (m, 21 H), 7.20–7.18 (m, 3 H), 7.03 (d, J = 2.4 Hz, 2 H), 6.96–6.93 (m, 2 H), 6.92 (d, J = 2.0 Hz, 1 H), 6.80 (t, J = 2.4 Hz, 1 H), 6.52 (d, J = 2.4 Hz, 1 H), 5.09

(s, 2 H), 4.98 (s, 4 H), 4.85 (s, 2 H), 4.67 (s, 2 H) 1.00 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 160.9, 160.0, 157.5, 142.3, 141.1, 136.8, 136.7, 136.5, 135.6, 133.4, 129.8, 128.8, 128.8, 128.4, 128.3, 128.2, 127.8, 127.7, 127.7, 127.0, 120.3, 108.2, 107.1, 105.0, 99.7, 70.4, 70.3, 70.3, 63.5, 26.9, 19.4; HRMS (FAB+) calcd for $C_{58}H_{54}O_6^+Si$ [M^+] 874.3643, found 874.3673.

Aldehyde 116. To a suspension of trimethylsulfonium iodide (15.0 g, 73.8 mmol, 6.0 equiv) in THF (150 mL) at 0 °C was added *n*-BuLi (36.1 mL, 1.6 M in hexanes, 57.7 mmol, 5.0 equiv). After stirring the resulting opaque pale yellow solution for 3 min at 0 °C, a solution of **115** (10.1 g, 11.5 mmol, 1.0 equiv) in THF (100 mL) was added via cannula over the course of 2 min. The reaction mixture was then warmed to 25 °C and stirred for 1 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (80 mL), poured into water (50 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layers were then washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. Pressing forward without any further purification, the so-obtained crude epoxide was taken up in benzene (80 mL) and ZnI_2 (3.68 g, 11.5 mmol, 1.0 equiv) was added as a single portion at 25 °C in an ambient atmosphere. Upon completion (generally 10–15 min as judged by careful TLC analysis), the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL), poured into water (100 mL), and extracted with EtOAc (3 × 60 mL). The combined organic layers were then washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to give **116** (10.3 g, 11.5 mmol, 100% yield assumed) as an orange foam. Generally, this material was carried forward without any further purification. For characterization purposes, however, the resultant yellow/orange crude oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) to give **116** as a white foam. **116**: R_f = 0.63 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3032, 2930, 2858, 1724, 1603, 1454, 1376, 1299, 1152, 1112, 1057, 824,

738, 699, 609, 504 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1 H), 7.66–7.64 (m, 2 H), 7.61–7.59 (m, 2 H), 7.44–7.21 (m, 26 H), 6.79 (d, *J* = 2.4 Hz, 1 H), 6.61 (d, *J* = 2.4 Hz, 1 H), 6.49 (t, *J* = 2.2 Hz, 1 H), 6.36 (d, *J* = 2.2 Hz, 2 H), 5.03 (s, 2 H), 4.98 (d, *J* = 11.8 Hz, 1 H), 4.94 (d, *J* = 11.8 Hz, 1 H), 4.87 (d, *J* = 11.5 Hz, 1 H), 4.83 (d, *J* = 11.5 Hz, 1 H), 4.75 (d, *J* = 13.1 Hz, 1 H), 4.72 (s, 1 H), 4.58 (d, *J* = 13.1 Hz, 1 H), 1.04 (s, 9 H);); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 160.1, 159.5, 157.0, 142.4, 139.5, 137.0, 137.0, 136.3, 135.7, 133.4, 133.2, 129.9, 128.8, 128.7, 128.7, 128.1, 127.9, 127.9, 127.7, 127.7, 127.6, 117.4, 108.2, 106.3, 100.9, 100.3, 70.9, 70.3, 70.1, 64.3, 56.3, 26.9, 19.4; HRMS (FAB+) calcd for $C_{59}H_{56}O_6{}^+Si$ [M^+] 888.3846, found 888.3842.

Alcohol 117. Crude aldehyde **116** (10.3 g, 11.5 mmol, 1.0 equiv) was dissolved in THF (80 mL) and 4-benzyloxyphenylmagnesium bromide (12.7 mL, 1.0 M in THF, 12.7 mmol, 1.1 equiv) was added at 25 °C. After stirring for 10 min at 25 °C, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (20 mL), poured into water (30 mL), and extracted with EtOAc (3 × 60 mL). The combined organic layers were then washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant crude material by flash column chromatography (silica gel, hexanes/EtOAc 9:1→5:1) gave benzylic alcohol **117** (9.15 g, 74 % yield from **115**, 1:1 mixture of diastereomers) as a pale yellow oil.

Dihydrobenzofuran 118. To a solution of benzylic alcohol **117** (4.80 g, 4.5 mmol, 1.0 equiv) in EtOAc (40 mL) at 25 °C was sequentially added 10% Pd/C (2.38 g, 2.25 mmol, 0.5 equiv Pd), $NaHCO_3$ (77.0 mg, 0.92 mmol, 0.2 equiv), and MeOH (60 mL). H_2 gas was then bubbled through the reaction mixture for 30 min, after which time the reaction contents were stirred at 25 °C under a H_2 atmosphere (1 atm) for 6 h. Upon completion, the reaction mixture was filtered by vacuum filtration using filter paper (Whatman 1) and a Buchner funnel. The

filtrate was concentrated, taken up in MeOH (100 mL), and HCl (22.5 mL, 1.25 M in MeOH, 18.0 mmol, 4.0 equiv) was added. The resultant solution was then stirred at 25 °C in an ambient atmosphere for 6 h, after which time the contents were concentrated directly. The resultant crude product was taken up acetone (80 mL) and K_2CO_3 (7.40 g, 53.5 mmol, 12 equiv), benzyl bromide (4.30 mL, 35.8 mmol, 8.0 equiv) and *n*-Bu_4NI (0.830 g, 2.25 mmol, 0.5 equiv) were added sequentially in an ambient atmosphere at 25 °C. The reaction flask was then sealed with a plastic cap to prevent solvent evaporation and allowed to stir for 12 h at 25 °C. Upon completion, the reaction contents were quenched by the addition of water (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude residue was purified by flash column chromatography (silica gel, hexanes/EtOAc 9:1→5:1) to afford **118** (2.36 g, 73% yield) as a yellow foam along with the *cis*-disposed dihydrofuran-containing isomer **S3** (0.240 g, 7% yield). [Note: Solid $NaHCO_3$ was used in the hydrogenation to buffer the relatively high acidity of the palladium catalyst used. The progress of this hydrogenation varied heavily with different bottles of palladium catalyst and needed to be reinvestigated with each new bottle.] **118**: R_f = 0.44 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3562, 3033, 2923, 2870, 1591, 1511, 1495, 1452, 1377, 1338, 1293, 1264, 1241, 1153, 1130, 1080, 1047, 1026, 910, 828, 733, 695, 634, 567, 522, 458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.31 (m, 20 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 6.94 (d, *J* = 8.4 Hz, 2 H), 6.60 (d, *J* = 2.0 Hz, 1 H), 6.56 (d, *J* = 2.0 Hz, 1 H), 6.55 (t, *J* = 2.0 Hz, 1 H), 6.38 (d, *J* = 2.0 Hz, 2 H), 5.47 (d, *J* = 6.0 Hz, 1 H), 5.09 (s, 2 H), 5.07 (s, 2 H), 5.01 (d, *J* = 11.6 Hz, 2 H), 4.97 (d, *J* = 11.6 Hz, 2 H), 4.41 (d, *J* = 6.4 Hz, 1 H), 4.17 (dd, *J* = 13.2, 7.2 Hz, 1 H), 4.11 (dd, *J* = 13.2, 5.2 Hz, 1 H), 1.19 (dd, *J* = 7.2, 5.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 160.7, 160.5, 158.9, 145.4, 138.8, 137.1, 137.1, 136.8, 133.9, 128.7, 128.2,

127.7, 127.7, 127.6, 127.0, 119.1, 115.2, 107.0, 106.7, 101.0, 96.2, 93.3, 70.5, 70.2 (2 C), 62.6, 56.6 (4 carbons buried in benzyl region); HRMS (FAB+) calcd for $C_{49}H_{42}O_6^+$ [M^+] 726.2981, found 726.2985. **S3**: R_f = 0.40 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3445, 3033, 2871, 1592, 1512, 1495, 1452, 1376, 1341, 1291, 1265, 1240, 1146, 1132, 1080, 1045, 1026, 912, 832, 733, 696, 634, 545, 522, 457 cm^{-1}; ^1H NMR ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.26 (m, 20 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 6.71 (d, *J* = 8.8 Hz, 2 H), 6.65 (d, *J* = 2.0 Hz, 1 H), 6.60 (d, *J* = 2.4 Hz, 1 H), 6.28 (t, *J* = 2.0 Hz, 1 H), 5.90 (d, *J* = 8.4 Hz, 1 H), 5.86 (d, *J* = 2.0 Hz, 2 H), 5.12 (s, 2 H), 4.95 (s, 2 H), 4.80 (d, *J* = 12.0 Hz, 2 H), 4.75 (d, *J* = 12.0 Hz, 2 H), 4.60 (d, *J* = 8.4 Hz, 1 H), 4.33 (d, *J* = 13.6 Hz, 1 H), 4.25 (d, *J* = 13.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 160.5, 159.5, 158.2, 141.4, 138.9, 137.1, 137.1, 137.0, 129.5, 128.8, 128.7, 128.7, 128.2, 128.0, 128.0, 127.7, 127.6, 127.6, 120.2, 114.2, 108.4, 106.8, 101.2, 96.6, 89.6, 70.5, 70.1, 62.9, 52.1 (2 carbons buried in benzyl region; HRMS (FAB+) calcd for $C_{49}H_{42}O_6^+$ [M^+] 726.2981, found 726.3005.

Aldehyde S4. Dess–Martin periodinane (0.700 g, 1.65 mmol, 1.2 equiv) was added to a solution of alcohol **118** (1.00 g, 1.38 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at 25 °C, and the resultant mixture was stirred for 30 min in an ambient atmosphere. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous Na_2SO_3 (10 mL) and stirred vigorously for 5 min at 25 °C. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated and to give **S4** (0.997 g, quantitative yield assumed) as a yellow/orange foam which was carried on without further purification. **S4**: R_f = 0.59 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3033, 2923, 2854, 1695, 1607, 1589, 1511, 1496, 1454,

1378, 1341, 1306, 1264, 1242, 1137, 1080, 1051, 1026, 911, 829, 734, 695, 633, 566, 522, 458 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1 H), 7.48–7.31 (m, 20 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 7.03 (d, *J* = 2.4 Hz, 1 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 2.0 Hz, 1 H), 6.52 (t, *J* = 2.4 Hz, 1 H), 6.36 (d, *J* = 2.4 Hz, 2 H), 5.56 (d, *J* = 5.2 Hz, 1 H), 5.13 (s, 2 H), 5.07 (s, 2 H), 4.99 (d, *J* = 11.6 Hz, 2 H), 4.95 (d, *J* = 11.2 Hz, 2 H), 4.78 (d, *J* = 5.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 162.4, 160.7, 160.5, 159.0, 146.0, 136.9, 136.8, 136.5, 133.4, 133.2, 128.8, 128.8, 128.7, 128.4, 128.2, 128.2, 127.8, 127.8, 127.6, 127.0, 123.9, 115.2, 107.8, 107.0, 103.0, 100.6, 93.9, 70.8, 70.2, 70.2, 56.0; HRMS (FAB+) calcd for $C_{49}H_{40}O_6^+$ [M^+] 724.2825, found 724.2809.

Carboxylic Acid 119. To crude aldehyde **S4** (0.997 g, 1.38 mmol, 1.0 equiv) was added THF (15 mL), *t*-BuOH (15 mL), and 2-methyl-2-butene (2.90 mL, 27.5 mmol, 20 equiv) at 25 °C under an ambient atmosphere. A solution of NaH_2PO_4 (1.72 g, 11.0 mmol, 8.0 equiv) in water (7 mL) and a solution of $NaClO_2$ (0.371 g, 4.1 mmol, 3.0 equiv) in water (7 mL) were then added sequentially. After stirring the resultant mixture at 25 °C for 12 h, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (10 mL), poured into water (15 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with saturated aqueous brine (30 mL), dried ($MgSO_4$), filtered, and concentrated to give the desired carboxylic acid **119** (1.02 g, 100% yield assumed) as a yellow/orange foam which was carried on without further purification. **119**: R_f = 0.31 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3064, 3033, 2924, 2855, 1693, 1590, 1511, 1495, 1453, 1378, 1291, 1242, 1156, 1123, 1081, 1026, 911, 830, 735, 696, 633, 565, 524, 460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.26 (m, 20 H), 7.26 (d, *J* = 1.6 Hz, 1 H), 7.21 (d, *J* = 8.8 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 6.89 (d, *J* = 2.0 Hz, 1 H), 6.51 (t, *J* = 2.0 Hz, 1 H), 6.38 (d, *J* = 2.0 Hz, 1 H), 5.56 (d, *J* = 3.6 Hz, 1 H), 5.08 (s, 4

H), 4.97 (t, J = 12 Hz, 4 H), 4.86 (d, J = 3.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 162.2, 160.1 (3 C), 158.8, 146.7, 137.0, 136.9, 136.5, 134.2, 128.8, 128.7, 128.7, 128.3, 128.1, 128.1, 127.8, 127.8, 127.5, 127.0, 126.7, 124.6, 115.2, 109.4, 106.9, 102.5, 100.4, 93.1, 70.6, 70.2, 70.1, 57.1; HRMS (FAB+) calcd for $C_{49}H_{40}O_7^+$ [M^+] 740.2774, found 740.2781.

Ester 121. To a solution of the crude carboxylic acid **119** (1.02 g, 1.38 mmol, 1.0 equiv) obtained above in acetone (30 mL) at 25 °C was sequentially added bromide **120** (see later for synthesis, 0.628 g, 1.52 mmol, 1.1 equiv), K_2CO_3 (0.954 g, 6.90 mmol, 5.0 equiv), and *n*-Bu_4NI (52 mg, 0.14 mmol, 0.1 equiv). The resultant reaction mixture was heated to 56 °C and stirred for 2 h before being quenched by the addition of water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc 9:1→4:1) to give **121** (1.20 g, 81% yield from **118**) as a white foam. **121**: R_f = 0.56 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3064, 3033, 2926, 1721, 1588, 1511, 1496, 1453, 1374, 1324, 1289, 1238, 1152, 1121, 1081, 1050, 1024, 925, 830, 736, 696, 632, 564, 522, 459 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.30 (m, 20 H), 7.28 (d, J = 2.4 Hz, 1 H), 7.20 (d, J = 8.8 Hz, 2 H), 6.92 (d, J = 8.4 Hz, 2 H), 6.82 (d, J = 2.4 Hz, 1 H), 6.76 (d, J = 2.8 Hz, 1 H), 6.53 (d, J = 2.8 Hz, 1 H), 6.45 (t, J = 2.0 Hz, 1 H), 6.24 (d, J = 2.0 Hz, 2 H), 5.46 (d, J = 4.0 Hz, 1 H) 5.20 (d, J = 13.2 Hz, 1 H), 5.14 (s, 2 H), 5.12 (s, 2 H), 5.02 (s, 2 H), 5.01 (d, J = 14.4 Hz, 1 H), 4.88 (s, 7 H), 3.45 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 162.3, 160.2, 158.9, 158.8, 154.8, 146.7, 137.1, 137.0, 137.0, 136.6, 136.5, 134.0, 128.8, 128.7, 128.7, 128.7, 128.6, 128.3, 128.2, 128.1, 128.1, 128.0, 127.8, 127.8, 127.8, 127.6, 127.0, 123.3, 115.2, 109.4, 108.7, 106.6, 104.7, 103.7, 101.8, 100.4, 95.4, 93.1, 70.7, 70.4, 70.2, 70.1, 66.3, 57.3, 56.5; LRMS (FAB+) calcd for $C_{65}H_{55}BrO_{10}^+$ [M^+] 1076.3, found 1076.2.

Ketone 122. To a solution of ester **121** (2.00 g, 1.86 mmol, 1.0 equiv) in THF (100 mL) at –94 °C was added *n*-BuLi (1.40 mL, 1.6 M in hexanes, 2.24 mmol, 1.1 equiv) dropwise over the course of 15 min. The reaction mixture was then stirred for an additional 20 min at –94 °C, with TLC indicating the presence of residual starting material. Additional *n*-BuLi (0.45 mL, 1.6 M in hexanes, 0.74 mmol, 0.4 equiv) was then added dropwise in 3 equal portions at 20 min intervals until the consumption of **121** was verified by TLC analysis. Next, the cold bath was removed and the reaction contents were allowed to warm for 30 min, at which point TBDPSCl (1.95 mL, 7.50 mmol, 4.0 equiv) and DBU (0.28 mL, 1.86 mmol, 1.0 equiv) were added sequentially. The reaction mixture was then warmed at 50 °C for 12 h. Upon completion, the reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), poured into water (30 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with brine (100 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 5:1) to give **122** (1.84 g, 80% yield) as a yellow foam. **122**: R_f = 0.59 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3033, 2929, 2858, 1720, 1667, 1587, 1510, 1454, 1432, 1378, 1320, 1243, 1151, 1112, 1081, 1026, 928, 826, 738, 698, 608, 505 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61–7.55 (m, 4 H), 7.44–7.26 (m, 31 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 2.0 Hz, 1 H), 6.75 (d, *J* = 2.4 Hz, 1 H), 6.71 (d, *J* = 2.0 Hz, 1 H), 6.44 (t, *J* = 2.0 Hz, 1 H), 6.33 (br s, 2 H), 5.47 (d, *J* = 4.4 Hz, 1 H), 5.06 (s, 2 H), 5.04 (s, 2 H), 4.93 (s, 7 H), 4.65–4.56 (m, 4 H), 2.97 (s, 3 H), 0.95 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 162.1, 160.9, 160.1, 160.0, 158.8, 156.5, 146.5, 142.6, 137.1, 137.0, 137.0, 136.7, 136.7, 135.6, 134.3, 133.5, 133.4, 129.8, 129.7, 128.7, 128.7, 128.7, 128.3, 128.2, 128.1, 128.1, 127.8, 127.7, 127.6, 127.1, 121.5, 120.6, 115.2, 111.2, 107.2, 106.2, 100.9,

100.5, 99.9, 94.1, 93.4, 70.6, 70.2, 70.2, 70.1, 63.5, 56.5, 55.8, 26.9, 19.4 (1 carbon buried in benzyl region); LRMS (FAB+) calcd for $C_{81}H_{74}O_{10}Si^{+}$ [M^{+}] 1234.51, found 1234.71.

Aldehyde 123. To a suspension of trimethylsulfonium iodide (3.34 g, 16.4 mmol, 10 equiv) in THF (50 mL) at 0 °C was added *n*-BuLi (8.18 mL, 1.6 M in hexanes, 13.1 mmol, 8.0 equiv). After stirring the resultant opaque pale yellow solution for 3 min at 0 °C, a solution of **122** (2.02 g, 1.64 mmol, 1.0 equiv) in THF (15 mL) was then added over the course of 2 min. Once the addition was complete, the cold bath was removed, the reaction mixture allowed to warm to 25 °C, and the contents were stirred for 1 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (15 mL), poured into water (20 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. Pressing forward without any further purification, the resultant crude epoxide was dissolved in benzene (40 mL) and ZnI_2 (1.56 g, 4.91 mmol, 3.0 equiv) was added as a single portion at 25 °C in an ambient atmosphere. After stirring the reaction contents for 20–25 minutes at 25 °C (careful monitoring by TLC), the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL), poured into water (30 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated to afford the desired aldehyde (**123**, 2.04 g, quantitative yield assumed) that was normally carried forward without any further purification. Analytically pure aldehyde **123** (as a 1:1 mixture of diastereomers) could be obtained via flash column chromatography (silica gel, hexanes/EtOAc, 9:1). **123**: R_f = 0.57 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3054, 2932, 1727, 1605, 1592, 1512, 1454, 1378, 1298, 1265, 1146, 1028, 925, 827, 732, 700, 634, 610, 504 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1:1 ratio of diastereomers) δ 9.36 (s, 1 H), 9.13 (s, 1 H), 7.59 (d, J = 6.9 Hz, 2 H), 7.53

(d, J = 7.1 Hz, 2 H), 7.49–7.26 (m, 64 H), 7.18 (t, J = 7.5 Hz, 2 H), 7.12 (d, J = 7.5 Hz, 2 H), 6.99 (d, J = 8.6 Hz, 2 H), 6.95 (d, J = 1.9 Hz, 1 H), 6.89 (s, 4 H), 6.79 (d, J = 2.2 Hz, 1 H), 6.76 (d, J = 2.2 Hz, 2 H), 6.58 (d, J = 1.8 Hz, 1 H), 6.53 (d, J = 1.9 Hz, 1 H), 6.47 (br s, 1 H), 6.41 (br s, 1 H), 6.24 (br s, 2 H), 6.05 (br s, 2 H), 5.87 (d, J = 1.7 Hz, 1 H), 5.44 (d, J = 6.4 Hz, 1 H), 5.43 (d, J = 7.5 Hz, 1 H), 5.12 (s, 4 H), 5.07 (d, J = 6.8 Hz, 1 H), 5.05 (s, 2 H), 5.04 (d, J = 7.3 Hz, 1 H), 5.00 (br s, 2 H), 4.95 (br s, 4 H), 4.92 (d, J = 6.2 Hz, 2 H), 4.89 (s, 1 H), 4.88 (d, J = 10.8 Hz, 2 H), 4.82 (br s, 4 H), 4.53 (d, J = 13.8 Hz, 1 H), 4.44 (d, J = 3.5 Hz, 1 H), 4.42 (s, 1 H), 4.40 (d, J = 13.6 Hz, 1 H), 4.32 (d, J = 13.4 Hz, 1 H), 4.23 (d, J = 13.4 Hz, 1 H), 4.13 (s, 1 H), 3.98 (d, J = 7.5 Hz, 1 H), 3.42 (s, 3 H), 3.27 (s, 3 H), 1.06 (s, 9H), 0.99 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, 1:1 ratio of diastereomers) δ 197.3, 197.3, 161.0, 160.9, 160.6, 160.3, 160.2, 159.5, 159.3, 159.0, 158.8, 156.2, 155.3, 144.7, 144.1, 142.9, 142.0, 137.1, 137.0, 137.0, 137.0, 137.0, 136.9, 135.8, 135.8, 135.7, 135.6, 135.4, 134.2, 133.6, 133.3, 133.2, 133.0, 132.9, 130.1, 129.9, 129.7, 129.7, 128.8, 128.7, 128.7, 128.7, 128.6, 128.6, 128.6, 128.1, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 127.1, 121.5, 121.4, 117.2, 115.1, 115.1, 114.4, 108.8, 108.2, 107.6, 107.5, 107.3, 106.1, 101.5, 101.3, 101.3, 101.2, 96.0, 95.7, 94.9, 94.3, 93.6, 93.4, 70.2, 70.2, 70.2, 70.1, 69.9, 63.7 63.3, 57.3, 57.1, 56.5, 56.2, 53.6, 53.0, 27.0, 27.0, 19.4, 19.4; LRMS (FAB+) calcd for $C_{82}H_{74}O_{10}Si^+$ [M^+] 1248.5, found 1248.9.

Ketone 124. To a solution of crude aldehyde **123** (2.04 g, 1.63 mmol, 1.0 equiv) in THF (40 mL) at 0 °C was added 4-benzyloxyphenylmagnesium bromide (1.96 mL, 1.0 M in THF, 1.96 mmol, 1.2 equiv) dropwise over the course of 2 min. After the addition was complete, the cold bath was removed and the reaction mixture was warmed to 25 °C over the course of 10 min. The reaction contents were then quenched by the addition of saturated aqueous NH_4Cl (10 mL), poured into water (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic

layers were then washed with brine (30 mL), dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1→4:1) to give the resulting benzylic alcohol as a mixture of 4 diastereomers. This mixture of products was then dissolved in CH_2Cl_2 (40 mL) and Dess–Martin periodinane (0.831 g, 1.96 mmol, 1.2 equiv) was added in a single portion at 25 °C in an ambient atmosphere. After stirring at 25 °C for 30 min, the reaction contents were quenched by the addition of saturated aqueous Na_2CO_3 (10 mL), poured into saturated aqueous $NaHCO_3$ (20 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1→4:1) to give the desired benzylic ketone **124** (1.92 g, 82% from **122**) as a pale yellow foam and a 1:1 mixture of diastereomers.

Benzofuran Atropisomers 125 and 126. The diastereomeric mixture of compound **124** (1.92 g, 1.34 mmol, 1.0 equiv) was dissolved in THF (40 mL) and MeOH (20 mL) and HCl (21.5 mL, 1.25 M in MeOH, 26.8 mmol, 20 equiv) were added sequentially at 25 °C in an ambient atmosphere. The reaction contents were then warmed to 40 °C and stirred for 12 h. Upon completion, the reaction mixture was concentrated directly, redissolved in THF (30 mL), and TBAF (1.60 mL, 1.0 M in THF, 1.60 mmol, 1.2 equiv) was added at 25 °C. The reaction contents were then warmed to 50 °C ans stirred for 12 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (10 mL), poured into water (10 mL), and extracted with EtOAc (3 × 25 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) to give alcohols **125** and **126** (1.33 g, 88% yield) as a 1:1 mixture of atropisomers. Warming of this mixture in toluene at 80 °C for 24 h

afforded a 2.8:1 ratio of atropisomers from which **126** could be separated by flash column chromatography (silica gel chromatography, hexanes/EtOAc, 9:1) while the other, **125**, could not be obtained in pure form, with the major, separable isomer (**126**) being the one which was carried forward. **126**: R_f = 0.40 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3541, 3034, 2928, 2870, 1594, 1510, 1496, 1454, 1428, 1377, 1304, 1264, 1244, 1175, 1145, 1057, 1025, 913, 829, 732, 696, 634, 570, 505, 457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.31 (m, 32 H), 7.01 (d, *J* = 8.7 Hz, 2 H), 6.89 (d, *J* = 2.3 Hz, 1 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 6.85 (s, 1 H), 6.84 (d, *J* = 8.8 Hz), 6.69 (d, *J* = 2.2 Hz, 1 H), 6.61 (d, *J* = 2.2 Hz, 1 H), 6.01 (s, 3 H), 5.61 (d, *J* = 6.2 Hz, 1 H), 5.13 (d, *J* = 11.8 Hz, 1 H), 5.08 (d, *J* = 11.8 Hz, 1 H), 5.06 (s, 2 H), 4.98 (s, 2 H), 4.97 (s, 2 H), 4.69 (d, *J* = 11.2 Hz, 2 H), 4.63 (d, *J* = 11.2 Hz, 2 H), 4.12 (dd, *J* = 14.2, 8.4 Hz, 1 H), 3.99 (dd, *J* = 14.2, 4.0 Hz, 1 H), 3.84 (d, *J* = 6.2 Hz, 1 H), 1.48 (dd, *J* = 8.6, 3.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 160.7, 159.6, 158.9, 158.8, 157.1, 154.3, 149.5, 144.6, 137.2, 136.9, 136.9, 136.8, 136.8, 136.0, 133.5, 132.2, 128.8, 128.7, 128.7, 128.2, 128.2, 128.1, 128.1, 128.0, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.4, 127.1, 126.9, 124.4, 123.9, 120.5, 115.2, 115.0, 113.4, 110.0, 108.9, 107.1, 99.7, 97.8, 95.5, 92.6, 70.5, 70.4, 70.2, 70.1, 70.0, 61.4, 56.5; LRMS (FAB+) calcd for $C_{77}H_{62}O_9^+$ [M^+] 1130.44, found 1130.73.

Aldehyde 130. To a solution of benzofuran **126** (1.45 g, 1.27 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) at 25 °C was added Dess–Martin periodinane (0.645 g, 1.52 mmol, 1.2 equiv) in an ambient atmosphere. After stirring at 25 °C for 30 min, the reaction contents were quenched by the addition of saturated aqueous Na_2SO_3 (10 mL), poured into saturated aqueous $NaHCO_3$ (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc,

17:3) to give **130** (1.35 g, 93% yield) as a bright yellow foam. **130**: R_f = 0.53 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3064, 3033, 2926, 2867, 1682, 1608, 1510, 1484, 1454, 1378, 1354, 1304, 1246, 1176, 1146, 1082, 1058, 1024, 913, 831, 736, 696, 634, 570, 540, 459 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1 H), 7.49 (d, *J* = 9.2 Hz, 2 H), 7.41–7.31 (m, 31 H), 7.18 (d, *J* = 2.0 Hz, 1 H), 7.02 (d, *J* = 8.8 Hz, 2 H), 6.93 (d, *J* = 9.2 Hz, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 6.72 (d, *J* = 2.4 Hz, 1 H), 6.68 (d, *J* = 2.4 Hz, 1 H), 5.95 (d, *J* = 2.0 Hz, 2 H), 5.92 (t, *J* = 2.0 Hz, 1 H), 5.63 (d, *J* = 6.0 Hz, 1 H), 5.09 (s, 4 H), 4.99 (s, 4 H), 4.64 (d, *J* = 11.2 Hz, 2 H), 4.60 (d, *J* = 10.8 Hz, 2 H), 3.88 (d, *J* = 6.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 161.3, 161.2, 159.8, 159.4, 158.9, 156.3, 155.0, 152.0, 144.5, 136.9, 136.9, 136.6, 133.7, 132.1, 129.3, 128.8, 128.8, 128.7, 128.3, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.6, 127.2, 126.2, 124.3, 123.1, 115.3, 115.0, 112.7, 108.9, 108.0, 106.7, 103.5, 99.8, 92.7, 70.8, 70.7, 70.3, 70.1, 69.8, 56.7 (7 carbons buried in benzyl region); LRMS (FAB+) calcd for $C_{77}H_{60}O_9^+$ [M^+] 1128.4, found 1128.5.

Allylic Alcohol 131. Freshly prepared vinyllithium[1] (2.50 mL, ~1.0 M in THF, 2.50 mmol, 2.1 equiv) was added dropwise to a solution of aldehyde **130** (1.35 g, 1.20 mmol, 1.0 equiv) in THF (40 mL) at –78 °C. Upon completion (as indicated by the disappearance of the characteristic bright yellow color of aldehyde **130**), the reaction mixture was quenched at –78 °C by the addition of saturated aqueous NH_4Cl (10 mL), warmed to 25 °C, poured into water (15 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), and concentrated directly to give allylic alcohol **131** (1.38 g, 100% yield assumed) as a pale yellow foam and as a single diastereomer which was carried forward without any further purification. **131**: R_f = 0.53 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3512, 3034, 2926, 2857, 1605, 1510, 1496, 1454, 1425, 1377, 1304, 1264, 1244,

1176, 1143, 1024, 916, 830, 733, 696, 634, 570, 522, 456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.30 (m, 32 H), 7.01 (d, *J* = 8.7 Hz, 2 H), 6.98 (d, *J* = 2.2 Hz, 1 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 6.86 (d, *J* = 2.3 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.66 (d, *J* = 2.2 Hz, 1 H), 6.63 (d, *J* = 2.2 Hz, 1 H), 6.07 (d, *J* = 2.1 Hz, 2 H), 5.96 (t, *J* = 2.1 Hz, 1 H), 5.91 (ddd, *J* = 17.0, 10.6, 4.4 Hz, 1 H), 5.58 (d, *J* = 7.2 Hz, 1 H), 5.08 (s, 3 H), 5.07 (s, 2 H), 5.05 (br s, 1 H), 5.01 (d, *J* = 1.6 Hz, 2 H), 4.98 (s, 2 H), 4.95 (br s, 1 H), 4.71 (d, *J* = 11.6 Hz, 2 H), 4.68 (d, *J* = 11.6 Hz, 2 H), 3.84 (d, *J* = 7.6 Hz, 1 H), 2.56 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 160.6, 159.4, 158.9, 158.8, 157.1, 154.2, 149.8, 144.7, 139.9, 138.4, 137.2, 136.9, 136.8, 136.6, 133.2, 131.9, 128.8 128.8, 128.7, 128.7, 128.3, 128.2, 128.2, 128.1, 128.1, 127.8, 127.7, 127.6, 127.6, 127.5, 127.1, 124.3, 120.7, 115.3, 115.2, 115.0, 113.4, 109.8, 109.6, 107.6, 99.4, 97.8, 95.8, 92.8, 70.6, 70.5, 60.2, 70.2, 70.1, 68.9, 56.6 (3 carbons buried in benzyl region); LRMS (FAB+) calcd for $C_{79}H_{62}O_8^+$ [M-H_2O^+] 1138.4, found 1139.0.

Alkene 132. Methanesulfonic acid (5.60 mL, 86.2 mmol, 72 equiv) was added to a solution of allylic alcohol **131** (1.38 g, 1.2 mmol, 1.0 equiv) in THF (135 mL) at 25 °C in an ambient atmosphere. The resultant reaction mixture was then warmed to 50 °C and stirred for 45 min. Upon completion, the contents were removed from the heating bath, quenched carefully by the slow addition of saturated aqueous $NaHCO_3$ (25 mL), poured into water (25 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layers were then washed with brine (30 mL), dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 22:3) to give nine membered cylization product **132** (0.996 g, 73% yield from **130**) as a pale yellow foam. **132**: R_f = 0.55 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3034, 2925, 2857, 1608, 1509, 1454, 1418, 1378, 1299, 1244, 1176, 1139, 1066, 1024, 912, 828, 807, 734, 696, 634, 520, 457 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.8 Hz, 2 H), 7.48–7.28

(m, 30 H), 7.21 (d, *J* =7.0 Hz, 2 H), 7.11 (d, *J* = 1.8 Hz, 1 H), 7.01 (d, *J* =8.6 Hz, 2 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 2.0 Hz, 1 H), 6.85 Hz (ddd, *J* = 18.1, 10.4, 6.0 Hz, 1 H), 6.62 (d, *J* = 2.2 Hz, 1 H), 6.57 (d, *J* = 4.0 Hz, 1 H), 6.35 (d, *J* = 2.0 Hz, 1 H), 6.32 (d, *J* = 2.0 Hz, 1 H), 5.57 (d, *J* = 2.1 Hz, 1 H), 5.30 (d, *J* = 11.6 Hz, 1 H), 5.14 (d, *J* = 10.2 Hz, 1 H), 5.09 (s, 2 H), 5.06 (d, *J* = 11.8 Hz, 1 H), 5.03 (d, *J* = 11.6 Hz, 1 H), 5.02 (d, *J* = 11.5 Hz, 1 H), 4.92 (d, *J* = 11.7 Hz, 1 H), 4.91 (d, *J* = 11.8 Hz, 1 H), 4.87 (d, *J* = 11.5 Hz, 1 H), 4.85 (d, *J* = 11.0 Hz, 1 H), 4.83 (d, *J* = 11.5 Hz, 1 H), 4.78 (d, *J* = 11.4 Hz, 1 H), 4.52 (d, *J* = 11.3 Hz, 1 H), 4.30 (d, *J* = 11.3 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 160.2, 159.3, 158.6, 158.6, 157.2, 156.6, 154.2, 151.4, 138.8, 138.7, 137.3, 136.9, 136.9, 136.9, 136.8, 136.1, 132.6, 131.2, 129.2, 128.8, 128.7, 128.7, 128.6, 128.6, 128.6, 128.3, 128.2, 128.2, 128.2, 128.1, 128.0, 128.0, 127.8, 127.8, 127.7, 127.6, 127.6, 127.6, 127.5, 124.2, 123.6, 122.1, 121.3, 115.4, 115.1, 114.9, 114.7, 113.0, 111.5, 109.5, 100.8, 98.0, 94.6, 93.9, 70.5, 70.3, 70.3, 70.2, 70.1, 69.8, 60.5, 41.5; LRMS (FAB+) calcd for $C_{79}H_{62}O_8^+$ [M^+] 1138.4, found 1139.0.

Aldehyde 133. NMO (0.354 g, 3.0 mmol, 3.0 equiv) and OsO_4 (2.00 mL, 2.5 wt % in *t*-BuOH, 0.197 mmol, 0.2 equiv) were added sequentially to a solution of nine membered alkene **132** (1.13 g, 0.99 mmol, 1 equiv) in acetone (30 mL) and water (6 mL) at 25 °C in an ambient atmosphere. The reaction flask was sealed to prevent solvent evaporation and then allowed to stir at 25 °C for 8 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous Na_2SO_3 (10 mL), poured into water (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), concentrated, and carried forward without any further purification. Next, $NaIO_4$ on silica (7.00 g, 0.7 mmol/g, 4.90 mmol, 5.0 equiv) was added to a solution of the crude diol intermediate in CH_2Cl_2 (3 mL) at 25 °C in an ambient atmosphere. After stirring the resultant slurry at 25 °C for

1 h, the reaction mixture was filtered directly through a pad of Celite, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 5:1) to give aldehyde **133** (0.860 g, 76% from **S10**) as a pale yellow foam. **133**: R_f = 0.58 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3063, 3033, 2924, 2869, 2727, 1725, 1606, 1582, 1509, 1496, 1454, 1426, 1377, 1303, 1282, 1245, 1224, 1177, 1143, 1083, 1065, 1026, 1002, 914, 830, 735, 697, 635, 522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1 H), 7.49 (d, *J* = 8.8 Hz, 2 H), 7.46–7.27 (m, 30 H), 7.20 (dd, *J* = 7.6, 2.0 Hz, 2 H), 7.09 (d, *J* = 2.0 Hz, 1 H), 6.99 (d, *J* = 8.8 Hz, 2 H), 6.90 (d, *J* = 2.0 Hz, 1 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 6.59 (d, *J* = 2.4 Hz, 1 H), 6.39 (d, *J* = 2.4 Hz, 1 H), 6.32 (d, *J* = 2.4 Hz, 1 H), 6.20 (s, 1 H), 5.72 (d, *J* = 2.4 Hz, 1 H), 5.33 (d, *J* = 9.9 Hz, 1 H), 5.08 (s, 2 H), 5.05 (d, *J* = 1.8 Hz, 2 H), 5.04 (d, *J* = 11.4 Hz, 1 H), 4.95 (d, *J* = 9.9 Hz, 1 H), 4.91 (d, *J* = 11.6 Hz, 1 H), 4.90 (d, *J* =11.4 Hz, 1 H), 4.85 (d, *J* = 11.4 Hz, 1 H), 4.84 (d, *J* = 11.6 Hz, 1 H), 4.80 (d, *J* = 11.3 Hz, 1 H), 4.56 (d, *J* = 11.5 Hz, 1 H), 4.41 (d, *J* = 11.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 161.4, 160.9, 159.4, 158.8, 158.1, 157.2, 156.9, 154.4, 151.3, 139.1, 137.2, 136.9, 136.9, 136.7, 136.7, 135.9, 133.1, 132.9, 131.8, 129.1, 128.9, 128.8, 128.8, 128.7, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 128.1, 127.9, 127.7, 127.6, 127.6, 123.4, 121.8, 120.2, 115.0 (4 C), 114.6, 112.6, 112.1, 109.3, 100.3, 98.2, 95.6, 94.6, 71.1, 70.5, 70.4, 70.3, 70.2, 69.9, 58.8, 49.0 (5 carbons buried in benzyl region); LRMS (FAB+) calcd for $C_{78}H_{60}O_9^+$ [M^+] 1140.4, found 1140.8.

Hexa-aryl Alcohol 134. 4-benzyloxyphenylmagnesium bromide (2.10 mL, 1.0 M in THF, 2.10 mmol, 2.4 equiv) was added to a solution of aldehyde **133** (1.00 g, 0.88 mmol, 1.0 equiv) in THF (40 mL) at 0 °C. After stirring for 10 min at 0 °C, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (15 mL), poured into water (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with brine

(15 mL), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 88:12→5:1) to give the resulting benzylic alcohol **134** (1.11 g, 95% yield) as a mixture of diastereomers.

Caraphenol A (2). Pressing forward, this newly formed diastereomeric mixture of benzylic alcohols (**134**, 1.11 g, 0.84 mmol, 1.0 equiv) was dissolved in EtOAc (40 mL) and 10% Pd/C (1.78 g, 1.67 mmol, 2.0 equiv Pd) and MeOH (40 mL) were added sequentially at 25 °C. H_2 was then bubbled through the reaction mixture for 30 min after which time the contents were allowed to stir for 5 h at 25 °C under a H_2 atmosphere (1 atm) with bubbling for 20 min each hour. Upon completion, the reaction mixture was filtered by vacuum filtration using filter paper (Whatman 1) and a Buchner funnel. To the filtrate was added HCl (14.0 mL, 1.25 M in MeOH, 17.5 mmol, 21 equiv) and the resulting reaction mixture was concentrated and purified by flash column chromatrography (silica gel, $CHCl_3$/EtOAc/MeOH, 10:1:1) to give caraphenol A (**2**, 0.340 g, 60% yield) as a red/brown foam. [Note: upon performing this reaction at this scale, HCl some decomposition was observed, an outcome not observed on smaller scale. As such, the reaction conditions were adapted to use Amberlite-120H instead which proved more suitable to scale. This procedure is outlined next.] Alternatively, this newly formed diastereomeric mixture benzylic alcohols (**134**, 0.75 g, 0.56 mmol, 1.0 equiv) was dissolved in EtOAc (35 mL) and 10% Pd/C (1.80 g, 1.69 mmol, 3.0 equiv Pd) and MeOH (35 mL) were added sequentially at 25 °C. H_2 was then bubbled through the reaction mixture for 30 min after which time the contents were allowed to stir for 2.5 h at 25 °C under a H_2 atmosphere (1 atm) with bubbling for 20 min at each hour. Upon completion, the reaction mixture was filtered by vacuum filtration using filter paper (Whatman 1) and a Buchner funnel and concentrated directly. The crude residue was taken up in MeOH (25 mL), Amberlite-120H (2.50 g) was added, and the reaction mixture stirred vigorously

at 25 °C in ambient atmosphere for 1.5 h. The reaction contents were filtered through a pad of Celite, concentrated, and purified by flash column chromatography (silica gel, $CHCl_3$/EtOAc/MeOH, 10:1:1) to give caraphenol A (**2**, 0.317 g, 83% yield) as a light brown foam. [Note: The progress of this hydrogenation varied heavily with different bottles of palladium catalyst and needed to be reinvestigated with each new bottle.] **2**: $R_f = 0.75$ (silica gel, CH_2Cl_2/MeOH, 4:1); IR (film) ν_{max} 3307, 2927, 2856, 1613, 1515, 1432, 1364, 1173, 1135, 1114, 1077, 1054, 995, 917, 835, 778, 724, 688, 626, 570, 526 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.27 (d, J = 8.6 Hz, 2 H), 7.25 (d, J = 8.2 Hz, 2 H), 6.94 (d, J = 1.9 Hz, 1 H), 6.80 (d, J = 8.6 Hz, 2 H), 6.80 (d, J = 1.9 Hz, 1 H), 6.75 (d, J = 8.8 Hz, 2 H), 6.70 (d, J = 8.6 Hz, 2 H), 6.54 (d, J = 1.8 Hz, 1 H), 6.50 (d, J = 2.1 Hz, 1 H), 6.32 (d, J = 2.2 Hz, 1 H), 6.26 (br s, 1 H), 5.92 (s, 2 H), 4.86 (s, 1 H), 4.35 (s, 1 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.6, 160.6, 160.0, 159.1, 158.2, 158.1, 158.0, 157.1, 155.3, 149.6, 141.1, 139.8, 135.3, 133.7, 132.8, 128.3, 128.3, 127.5, 123.0, 122.9, 120.7, 119.2, 116.2, 116.0, 115.8, 114.6, 109.7, 108.7, 108.7, 98.4, 97.6, 96.4, 95.2, 88.0, 54.0, 46.0; HRMS (FAB+) calcd for $C_{42}H_{28}O_9^+$ [M^+] 676.1733, found 676.1720.

Ester 128. To a solution of methyl 3,5-dihydroxybenzoate **127** (5.45 g, 32.4 mmol, 1.0 equiv) in acetone (100 mL) at 25 °C in an ambient atmosphere was sequentially added K_2CO_3 (13.4 g, 97.2 mmol, 3.0 equiv), benzyl bromide (3.85 mL, 32.4 mmol, 1.0 equiv), and n-Bu_4NI (1.2 g, 3.2 mmol, 0.1 equiv) in single portions. The reaction contents were then heated to reflux (56 °C) and stirred for 12 h. Upon completion, the reaction mixture was cooled to 25 °C, quenched by the addition of water (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 19:1→4:1) to give the desired monobenzylated product (3.40 g, 41% yield) as a white solid. After repeating this

reaction, methyl 3-(benzyloxy-5)-hydroxybenzoate (22.0 g, 85.1 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (300 mL) and cooled to 0 °C. MOMCl (7.70 mL, 102 mmol, 1.2 equiv) was then added in a single portion followed by the dropwise addition of *i*-Pr_2NEt (28.4 mL, 170 mmol, 2.0 equiv) at 0 °C over the course of 5 min. The reaction mixture was then warmed to 25 °C and stirred for 30 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (100 mL), poured into water (50 mL), and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were then dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 5:1) to give ester **128** (22.3 g, 87% yield) as a colorless oil. **128**: R_f = 0.68 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3032, 2952, 1719, 1594, 1544, 1450, 1436, 1406, 1382, 1339, 1320, 1298, 1233, 1213, 1145, 1105, 1081, 1044, 1020, 923, 861, 766, 737, 697, 678, 641, 519, 459, 416 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.32 (m, 5 H), 7.34 (d, *J* = 2.4 Hz, 2 H), 6.89 (t, *J* = 2.4 Hz, 1 H), 5.19 (s, 2 H), 5.08 (s, 2 H), 3.90 (s, 3 H), 3.48 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 159.8, 158.3, 136.6, 132.2, 128.7, 128.2, 127.6, 110.2, 109.0, 108.6, 94.5, 70.4, 56.2, 52.3; HRMS (FAB+) calcd for $C_{16}H_{16}O_3^+$ [M^+] 302.1154, found 302.1158.

Bromide 129. $LiAlH_4$ (2.80 g, 73.9 mmol, 1.0 equiv) was added portionwise to a solution of **128** (22.3 g, 73.9 mmol, 1.0 equiv) in THF (300 mL) at 25 °C in an ambient atmosphere. After stirring at 25 °C for 5 min, the reaction mixture was quenched by the careful dropwise addition of water (10 mL), followed by saturated aqueous sodium potassium tartrate (400 mL); the resultant solution was then stirred vigorously at 25 °C for 1 h. Upon completion, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layers were then washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to give the desired benzylic alcohol (20.2 g, 99% yield) as a white solid.

Pressing forward without any further purification, the newly formed benzylic alcohol (20.2 g, 73.9 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (300 mL), cooled to 0 °C, and NBS (13.2 g, 72.9 mmol, 1.0 equiv) was added portionwise over the course of 30 min. The reaction mixture was then warmed to 25 °C and stirred for 12 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (100 mL), poured into water (50 mL), and extracted CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 × 100 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1→5:1) to give **129** (16.1 g, 62% yield) as a white solid. [Note: The regioisomeric bromination product (8.79 g, 34% yield) was also recovered and could be debrominated and recycled to enhance material throughput.] **129**: R_f = 0.45 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3392, 2900, 1586, 1496, 1445, 1400, 1380, 1321, 1280, 1215, 1150, 1097, 1050, 1015, 922, 840, 738, 699, 631, 550, 520, 508, 492, 460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 5 H), 6.85 (d, J =2.8 Hz, 1 H), 6.79 (d, J = 2.8 Hz, 1 H), 5.22 (s, 2 H), 5.06 (s, 2 H), 4.73 (d, J = 6.8 Hz, 2 H), 3.51 (s, 3 H), 1.99 (t, J = 6.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 154.6, 141.9, 136.6, 128.8, 128.3, 127.7, 108.0, 103.8, 103.2, 95.4, 70.5, 65.5, 56.5; HRMS (FAB+) calcd for $C_{16}H_{17}O_4^+$ [M^+] 352.0310, found 352.0298.

Benzyl Bromide 130. To a solution of Ph_3P (1.00 g, 3.80 mmol, 1.5 equiv) and imidazole (0.260 g, 3.80 mmol, 1.5 equiv) in CH_2Cl_2 (5 mL) at 0 °C was added Br_2 (0.20 mL, 3.80 mmol, 1.5 equiv) dropwise. The resultant reaction solution was warmed to 25 °C, stirred for 10 min, and then cooled back down to 0 °C. A solution of **129** (0.900 g, 2.60 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was then added, after which time the cold bath was removed and the reaction mixture allowed to warm to 25 °C. After stirring for 20 min at 25 °C, the reaction

mixture was concentrated directly and purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) to give **130** (1.05 g, 99% yield) as a white solid. **130**: R_f = 0.74 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2930, 2826, 1583, 1496, 1450, 1399, 1381, 1323, 1280, 1212, 1150, 1092, 1060, 1021, 924, 839, 735, 698, 640, 567, 546, 523, 506, 482, 462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.35 (m, 5 H), 6.83 (d, *J* = 2.4 Hz, 1 H), 6.80 (d, *J* = 2.4 Hz, 1 H), 5.22 (s, 2 H), 5.05 (s, 2 H), 4.60 (s, 2 H), 3.52 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 155.1, 138.6, 136.3, 128.7, 128.2, 127.6, 110.2, 106.2, 104.0, 95.3, 70.4, 56.5, 33.9; HRMS (FAB+) calcd for $C_{16}H_{16}O_3^+$ [M^+] 413.9466, found 413.9451.

13-Membered Ring 136. Dess–Martin periodinane (15.0 mg, 0.036 mmol, 1.2 equiv) was added to a solution of alcohol **108a** (20.0 mg, 0.030 mmol, 1.0 equiv) in CH2Cl2 (2 mL) at 25 °C, and the resultant slurry was stirred at 25 °C for 30 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous Na2SO3 (2 mL), stirred vigorously for 5 min, poured into saturated aqueous NaHCO3 (4 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with brine (5 mL), dried (MgSO4), and concentrated to give the desired aldehyde (20.0 mg, 99% yield) as a pale yellow oil. To a solution of this aldehyde (17.0 mg, 0.025 mmol, 1.0 equiv) in THF (1 mL) at 25 °C was added vinylmagnesium bromide (0.1 mL, 1.0 M in THF, 0.10 mmol, 4.0 equiv) and the resulting mixture was stirred at 25 °C for 10 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH4Cl (1 mL), poured into water (2 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with brine (3 mL), dried (MgSO4), concentrated, and purified by preparative TLC (hexanes/EtOAc, 7:3) to give **135** (11.0 mg, 62% yield) as a pale yellow oil (the balance of the material was recovered as alcohol **108a** resulting from aldehyde reduction). Pressing forward, methanesulfonic acid (0.04 mL, 0.55

mmol, 50 equiv) was added to a solution of **135** (8.0 mg, 0.011 mmol, 1.0 equiv) in THF (1 mL) at 25 °C in an ambient atmosphere, and the resultant mixture was allowed to stir at 50 °C for 1 h. Upon completion, the reaction mixture was quenched carefully by the slow addition of saturated aqueous NaHCO3 (1 mL), poured into water (1 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with brine (2 mL), dried (MgSO4), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) to give **136** (5.5 mg, 71% yield) as a pale yellow oil. **136**: R_f = 0.27 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2956, 2927, 2852, 1611, 1509, 1487, 1464, 1441, 1429, 1377, 1331, 1296, 1251, 1194, 1179, 1148, 1134, 1114, 1069, 1034, 965, 830; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.54 (d, *J* = 1.7 Hz, 1 H), 7.09 (dd, *J* = 8.2, 2.4 Hz, 1 H), 7.06 (d, *J* = 2.3 Hz, 1 H), 6.96 (d, *J* = 9.1 Hz, 2 H), 6.88 (d, *J* = 2.0 Hz, 1 H), 6.81 (d, *J* = 8.2 Hz, 1 H), 6.65 (d, *J* = 2.2 Hz, 1 H), 6.54 (d, *J* = 16.0 Hz, 1 H), 6.52 (d, *J* = 9.0 Hz, 2 H), 6.50 (d, *J* = 2.3 Hz, 1 H), 6.11 (ddd, *J* = 15.7, 9.4, 6.5 Hz, 1 H), 6.00 (d, *J* = 2.2 Hz, 2 H), 5.87 (t, *J* = 2.2 Hz, 1 H), 5.47 (d, *J* = 0.7 Hz, 1 H), 3.89 (s, 3 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.76 (s, 1 H), 3.75 (s, 3 H), 3.65 (dd, *J* = 13.0, 6.4 Hz, 1 H), 3.54 (s, 6 H), 2.89 (dd, *J* = 12.9, 9.4 Hz, 1 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 162.6, 162.5, 161.6, 159.9, 159.1, 158.0, 155.7, 151.3, 144.7, 135.9, 135.0, 134.8, 133.1, 131.7, 129.6, 129.5, 127.4, 126.2, 125.8, 123.9, 121.7, 113.9, 113.4, 110.8, 109.5, 109.3, 105.7, 98.8, 98.6, 95.4, 92.5, 57.1, 56.1 (2C), 55.9, 55.4, 55.2 (3C); HRMS (FAB+) calcd for $C_{43}H_{38}O_8^+$ [M^+] 682.2567, found 682.2587.

Alkyne 137. Pressing forward, the Ohira-Bestmann reagent (14.0 mg, 0.074 mmol, 2.0 equiv) was added to a solution of aldehyde **85** (25.0 mg, 0.037 mmol, 1.0 equiv) in MeOH/THF (2 mL, 1:1) followed by K2CO3 (51.0 mg, 0.37 mmol, 10.0 equiv) and the resultant mixture stirred for 12 h in an ambient atmosphere. Upon completion, the reaction mixture was quenched

by the addition of water (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were then dried (MgSO4), filtered, and concentrated to give **137** (25.0 mg, 99% yield) as a yellow oil which was carried forward without any further purification. **137**: R_f = 0.58 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3280, 3001, 2925, 2853, 1609, 1590, 1513, 1489, 1462, 1439, 1352, 1302, 1248, 1193, 1175, 1156, 1131, 1058, 1034, 990, 828, 785, 736, 692, 670, 634, 578, 538 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 6.58 (d, *J* = 8.8 Hz, 2 H), 6.54 (d, *J* = 8.6 Hz, 2 H), 6.49 (d, *J* = 2.3 Hz, 1 H), 6.49 (d, *J* = 2.3 Hz, 1 H), 6.42 (d, *J* = 1.9 Hz, 1 H), 6.21 (t, *J* = 2.2 Hz, 1 H), 6.19 (d, *J* = 2.2 Hz, 1 H), 6.16 (d, *J* = 2.0 Hz, 2 H), 5.49 (d, *J* = 3.5 Hz, 1 H), 5.38 (d, *J* = 3.5 Hz, 1 H), 4.51 (d, *J* = 3.6 Hz, 1 H), 4.20 (d, *J* = 3.5 Hz, 1 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.67 (s, 6 H), 2.07 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 161.4, 160.8, 160.8, 160.5, 159.4, 159.1, 147.1, 141.4, 135.2, 133.3, 126.5, 126.3, 120.6, 119.1 (2 C), 114.0, 113.8, 110.2, 106.0, 105.6, 99.1, 97.9, 94.4, 92.7, 92.5, 81.3, 80.5, 57.3, 55.8, 55.6, 55.5, 55.3, 55.3, 52.1; HRMS (FAB+) calcd for $C_{42}H_{38}O_8^+$ [M^+] 670.2567, found 670.2585.

Nine Membered Ring 138 and Seven Membered Ring 139. AuCl3 (2.4 mg, 0.074 mmol, 0.2 equiv) and AgOTf (6.2 mg, 0.22 mmol, 0.6 equiv) were added sequentially to 1,2-dichloroethane (1.0 mL) and stirred at 25 °C for 15 min. A solution of **137** (25.0 mg, 0.037 mmol, 1.0 equiv) in 1,2-dichloroethane (1.0 mL) was then added in a single portion and the reaction mixture was stirred at 25 °C for 30 min. Upon completion, the reaction mixture was filtered through a small silica gel plug eluting with EtOAc and concentrated directly after which the crude product was purified by preparative TLC (hexanes/acetone 3:2) to give **138** (2.0 mg, 8% yield) as a pale yellow oil and **139** (14.0 mg, 56% yield) as a pale yellow oil. **138**: IR (film) ν_{max} 2925, 2852, 1719, 1654, 1611, 1578, 1513, 1465, 1328, 1250, 1203, 1176, 1133, 1121,

1036, 994, 830, 605, 515, 494, 440, 417; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.76 (d, *J* = 2.2 Hz, 1 H), 6.73 (d, *J* = 2.0 Hz, 1 H), 6.67 (d, *J* = 8.8 Hz, 2 H), 6.65 (d, *J* = 2.2 Hz, 1 H), 6.42 (d, *J* = 2.1 Hz, 1 H), 6.34 (d, *J* = 2.1 Hz, 1 H), 6.18 (d, *J* = 2.2 Hz, 1 H), 5.96 (d, *J* = 12.9 Hz, 1 H), 5.89 (d, *J* = 1.1 Hz, 1 H), 5.83 (s, 1 H), 5.49 (d, *J* = 12.9 Hz, 1 H), 4.80 (d, *J* = 1.1 Hz, 1 H), 3.79 (s, 9 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.49 (s, 1 H), 3.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 161.0, 160.7, 160.0, 159.9, 159.4, 159.2, 158.2, 144.2, 140.6, 138.6, 137.1, 134.5, 133.7, 130.7, 128.2, 126.8, 125.1, 120.9, 120.4, 118.0, 114.1, 113.5, 105.0, 104.7, 102.3, 97.7, 97.1, 94.6, 89.0, 87.2, 55.9, 55.7, 55.6, 55.6, 55.4, 51.8, 46.3; HRMS (FAB+) calcd for $C_{42}H_{38}O_8^+$ [M^+] 670.2567, found 670.2590. **139**: R_f = 0.53 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3497, 3280, 3000, 2925, 2852, 1608, 1583, 1511, 1487, 1461, 1426, 1324, 1250, 1199, 1177, 1141, 1096, 1073, 1036, 1007, 965, 830, 736, 702, 631, 602, 573, 532; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.7 Hz, 2 H), 7.03 (d, *J* = 9.0 Hz, 2 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 6.74 (d, *J* = 2.8 Hz, 1 H), 6.73 (d, *J* = 8.9 Hz, 2 H), 6.39 (d, *J* = 2.1, 1 H), 6.31 (d, *J* = 2.1 Hz, 1 H), 6.28 (s, 2 H), 6.09 (d, *J* = 2.2, 1 H), 5.88 (d, *J* = 11.4 Hz, 1 H), 5.72 (s, 1 H), 5.49 (d, *J* = 3.4 Hz, 1 H), 4.79 (s, 1 H), 4.30 (d, *J* = 11.4 Hz, 1 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.72 (s, 3 H), 3.71 (s, 3 H), 3.70 (s, 3 H), 3.32 (s, 3 H), 3.24 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 160.2, 160.2, 160.0, 159.7, 158.8, 157.8, 156.8, 141.0, 137.5, 134.8, 130.2, 129.1, 127.7, 124.1, 123.8, 122.4, 119.4, 114.3, 113.8, 111.1, 108.1, 104.2, 103.8, 97.0, 96.1, 87.9, 82.7, 80.9, 56.3, 55.6, 55.5, 55.5 (2C), 55.2, 48.7, 43.7, 41.2; HRMS (FAB+) calcd for $C_{42}H_{39}O_8^+$ [M^+] 671.2797, found 671.2775.

Eleven Membered Ring 141, Nine Membered Ring 142, 13-Membered Ring 143, and Rearranged Allylic Alcohol S5. Methanesulfonic acid (0.15 mL, 2.3 mmol, 80 equiv) was added to a solution of allylic alcohol **140** (20.0 mg, 0.028 mmol, 1.0 equiv) in THF (3 mL) at 25

°C in an ambient atmosphere. The resultant reaction mixture was then warmed to 55 °C and stirred for 2 h. Upon completion, the contents were removed from the heating bath, quenched carefully by the slow addition of saturated aqueous NaHCO3 (3 mL), poured into water (3 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with brine (5 mL), dried (MgSO4), concentrated, and purified by preparative TLC (hexanes/EtOAc, 3:2) to give eleven membered cyclization product **141** (5.0 g, 26% yield) as a pale yellow oil, rearranged allylic alcohol **S5** (3.8 mg, 19% yield) as a pale yellow oil, and a third prep band (11 mg) that contained more than one compound; the contents of this band were derivatized (see below) and the products **142** and **143** of the above reaction retroactively identified. Eleven Membered Ring **141**: R_f = 0.68 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3000, 2926, 2838, 1612, 1579, 1512, 1460, 1421, 1338, 1303, 1248, 1188, 1172, 1126, 1112, 1033, 969, 829, 767, 735, 666, 632, 582, 539; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.6 Hz, 2 H), 6.99 (d, *J* = 8.6 Hz, 2 H), 6.97 (d, *J* = 8.6 Hz, 2 H), 6.74 (d, *J* = 8.7 Hz, 2 H), 6.44 (d, *J* = 2.2 Hz, 1 H), 6.42 (d, *J* = 2.2 Hz, 1 H), 6.36 (d, *J* = 2.1 Hz, 1 H), 6.32 (s, 2 H), 6.10 (dt, *J* = 15.9, 3.6 Hz, 1 H), 6.03 (d, *J* = 2.8 Hz, 1 H), 5.92 (d, *J* = 2.3 Hz, 1 H), 5.21 (d, *J* = 1.9 Hz, 1 H), 4.30 (d, *J* = 2.8 Hz, 1 H), 4.06 (d, *J* = 2.0 Hz, 1 H), 3.86 (s, 3 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.66 (d, *J* = 14.6 Hz, 1 H), 3.66 (s, 3 H), 3.55 (s, 3 H), 3.49 (d, *J* = 2.3 Hz, 2 H), 3.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 161.9, 161.4, 160.0, 159.9, 159.8, 159.5, 146.4, 142.2, 135.1, 134.9, 134.7, 132.3, 127.0, 126.9, 126.1, 122.5, 119.5, 116.5, 114.5, 114.2, 107.0, 106.8, 104.2, 101.4, 95.1, 94.4, 92.6, 90.6, 57.4, 56.4, 55.9, 55.6, 55.6, 55.5, 55.4, 50.6; HRMS (FAB+) calcd for $C_{43}H_{40}O_8^+$ [M^+] 684.2723, found 684.2706. **S5**: R_f = 0.27 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3516, 3000, 2955, 2934, 2838, 1611, 1590, 1587, 1513, 1486, 1463, 1436, 1342, 1304, 1295, 1248, 1202, 1195, 1174, 1157, 1135, 1066, 1057, 1033, 969, 829, 758, 736, 694, 617, 581, 538; ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.6 Hz, 2 H), 7.05 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* =8.7 Hz, 2 H), 6.68 (d, *J* = 8.7 Hz, 2 H), 6.57 (d, *J* = 2.2 Hz, 1 H), 6.47 (d, *J* = 2.2 Hz, 1 H), 6.35 (d, *J* = 2.2 Hz, 1 H), 6.27 (t, *J* = 2.2 Hz, 1 H), 6.16 (d, *J* = 2.2 Hz, 1 H), 6.08 (dt, *J* = 15.7, 5.5 Hz, 1 H), 5.94 (d, *J* = 2.2 Hz, 2 H), 5.87 (d, *J* = 15.9 Hz, 1 H), 5.31 (d, *J* = 5.2 Hz, 1 H), 5.16 (d, *J* = 8.4 Hz, 1 H), 4.28 (d, *J* = 8.5 Hz, 1 H), 4.05 (d, *J* = 14.8 Hz, 1 H), 3.97 (d, *J* = 16.3 Hz, 1 H), 3.84 (s, 3 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 3.72 (s, 3 H), 3.69 (s, 6 H), 3.47 (d, *J* = 5.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 161.9, 161.5, 161.1, 161.0, 159.9, 159.6, 145.6, 140.0, 134.9, 134.0, 132.7, 130.9, 128.0, 127.4, 126.8, 120.3, 118.7, 114.1, 114.1, 106.7, 106.2, 103.2, 98.2, 95.5, 94.8, 93.5, 92.9, 63.5, 56.4, 55.7 (2C), 55.5 (2C), 55.5, 55.3; HRMS (FAB+) calcd for $C_{43}H_{42}O_9^+$ [M^+] 702.2829, found 702.2803.

Nine Membered Ring Aldehyde S6 and Dialdehyde S7. NMO (7.5 mg, 0.064 mmol, 4.0 equiv) and OsO4 (0.033 mL, 2.5 wt % in *t*- BuOH, 0.0032 mmol, 0.2 equiv) were added sequentially to a solution of crude material containing **142** and **143** (11.0 mg, 0.016 mmol assumed, 1.0 equiv) in acetone (0.75 mL) and water (0.25 mL) at 25 °C in an ambient atmosphere. The reaction flask was sealed to prevent solvent evaporation and then allowed to stir at 25 °C for 8 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous Na2SO3 (1 mL), poured into water (2 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with brine (20 mL), dried (MgSO4), concentrated, and purified by preparative TLC (hexanes/EtOAc 2:3). Two bands from the preparative TLC (1.2 mg of Rf = 0.33, 1.9 mg of Rf = 0.21) were then carried forward separately. Next, $NaIO_4$ (1.8 mg, 0.0085 mmol, 5.0 equiv) and (2.8 mg, 0.013 mmol, 5.0 equiv) respectively were added to a solution of each of the crude diol intermediates in acetone (0.4 mL) and water (0.1 mL) at 25 °C in an ambient atmosphere. After stirring at 25 °C for 30 min, the

reaction mixture was quenched by the addition of saturated aqueous Na_2SO_3 (1 mL), poured into water (1 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were then washed with brine (2 mL), dried (MgSO4) and concentrated to give **S6** (1.8 mg, 9% yield from **140**) and **S7** (1.1 mg, 5% yield from **140**). **S6**: R_f = 0.65 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2956, 2925, 2853, 17.20, 1614, 1586, 1514, 1489, 1463, 1439, 1425, 1342, 1305, 1290, 1250, 1213, 1194, 1174, 1136, 1111, 1088, 1075, 1060, 1034, 979, 928, 829, 764, 734, 714; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1 H), 7.24 (d, *J* = 8.7 Hz, 2 H), 7.06 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 6.77 (d, *J* = 2.1 Hz, 1 H), 6.76 (d, *J* = 8.6 Hz, 2 H), 6.52 (d, *J* = 2.1 Hz, 1 H), 6.40 (d, *J* = 2.1 Hz, 1 H), 6.35 (d, *J* = 2.1 Hz, 1 H), 6.31 (d, *J* = 2.4 Hz, 1 H), 6.03 (d, *J* = 6.5 Hz, 1 H), 5.59 (d, *J* = 2.4 Hz, 1 H), 5.46 (s, 1 H), 5.25 (d, *J* = 11.6 Hz, 1 H), 4.71 (d, *J* = 11.7 Hz, 1 H), 4.54 (d, *J* = 6.5 Hz, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 3.64 (s, 3 H), 3.45 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 162.4, 160.5, 160.1, 159.6, 159.5, 159.3, 159.3, 139.3, 137.2, 136.2, 134.0, 130.4, 128.9, 127.2, 121.0, 120.8, 116.5, 114.2, 113.9, 107.9, 107.1, 105.5, 99.1, 95.6, 94.5, 94.0, 89.6, 70.8, 58.6, 55.7, 55.7, 55.6, 55.5, 55.4, 55.3, 51.2, 48.8; HRMS (FAB+) calcd for $C_{42}H_{38}O_9^+$ [M^+] 686.2516, found 686.2505. **S7**: R_f = 0.65 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2959, 2925, 1724, 1693, 1611, 1590, 1587, 1513, 1488, 1463, 1441, 1430, 1394, 1342, 1317, 1293, 1251, 1203, 1193, 1173, 1155, 1140, 1131, 1111, 1095, 1065, 1056, 1031, 983, 828, 804, 764, 735, 696, 623, 538; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 2.0 Hz, 1 H), 9.31 (s, 1 H), 7.07 (d, *J* = 8.6 Hz, 2 H), 7.03 (dd, *J* =8.5, 2.2 Hz, 1 H), 6.94 (d, *J* = 2.1 Hz, 1 H), 6.91 (d, *J* = 2.3 Hz, 1 H), 6.86 (d, *J* = 8.5 Hz, 1 H), 6.72 (d, *J* = 8.7 Hz, 2 H), 6.64 (d, *J* = 2.3 Hz, 1 H), 6.46 (d, *J* = 2.2 Hz, 1 H), 6.26 (t, *J* = 2.2 Hz, 1 H), 6.12 (d, *J* = 2.2 Hz, 1 H), 5.92 (d, *J* = 2.2 Hz, 2 H), 5.35 (d, *J* = 5.4 Hz, 1 H), 5.29 (d, *J* = 8.5 Hz, 1 H), 4.56 (d, *J* = 8.4 Hz, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.73 (s, 3 H), 3.72 (s, 3 H),

3.69 (s, 6 H), 3.65 (t, J = 2.6 Hz, 2 H), 3.55 (d, J = 5.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 189.9, 162.7, 162.2, 161.5, 161.4, 160.1, 157.7, 144.9, 134.0, 133.0, 131.9, 128.8, 128.4, 127.9, 126.2, 124.6, 121.8, 120.1, 114.2, 110.6, 106.2, 105.7, 103.6, 102.6, 99.4, 94.9, 94.2, 92.8, 56.5, 56.0, 55.7, 55.7, 55.4, 52.1, 49.6, 45.7; HRMS (FAB+) calcd for $C_{43}H_{40}O_{10}^+$ [M^+] 716.2621, found 716.2610.

Nine Membered Ring 145. PBr_3 (0.01 mL, 0.1 mmol, 10 equiv) and pyridine (1.0 μL, 0.12 mmol, 12 equiv) were added sequentially to a solution of **108** (7.6 mg, 0.01 mmol, 1.0 equiv) in Et_2O (1 mL) at 25 °C. The reaction mixture was then heated to reflux (35 °C) and stirred for 1 h. Upon completion, the reaction contents were quenched by the slow addition of water (1 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were then washed with brine (3 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 5:1) to give **145** (5.8 mg, 75% yield) as a pale yellow oil. **145**: IR (film) ν_{max} 2998, 2933, 2835, 1608, 1510, 1487, 1460, 1440, 1414, 1383, 1343, 1319, 1304, 1277, 1248, 1192, 1139, 1082, 1058, 1033, 981, 952, 898, 871, 828, 735, 702, 652, 631, 579, 550, 528, 508, 492, 467 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.9 Hz, 2 H), 7.25 (d, J = 9.1 Hz, 2 H), 6.95 (d, J = 2.2 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 2 H), 6.84 (d, J = 8.9 Hz, 2 H), 6.77 (d, J = 2.2 Hz, 1 H), 6.53 (d, J = 1.9 Hz, 1 H), 6.27 (d, J = 2.4 Hz, 1 H), 6.24 (d, J = 2.3 Hz, 1 H), 5.68 (d, J = 2.4 Hz, 1 H), 5.32 (d, J = 8.3 Hz, 1 H), 4.90 (d, J = 8.3 Hz, 1 H), 4.55 (d, J = 12.9 Hz, 1 H), 3.92 (d, J = 13.0 Hz, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.66 (s, 3 H), 3.41 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 161.3, 160.0, 159.4, 158.9, 157.8, 157.7, 154.5, 150.2, 138.8, 137.6, 133.4, 132.6, 128.6, 127.9, 123.6, 121.9, 121.5, 121.1, 115.3, 114.0 (4 C), 111.9, 110.6, 107.1, 98.0, 96.7, 94.8, 93.5, 58.1, 55.7, 55.7, 55.5, 55.5, 55.4, 54.9, 25.3; HRMS (FAB+) calcd for $C_{41}H_{36}O_8^+$ [M^+] 656.2410, found 656.2400.

Alcohol 154. To a solution of benzylic alcohol **117** (3.60 g, 3.35 mmol, 1.0 equiv) in EtOAc (40 mL) at 25 °C was sequentially added 10% Pd/C (2.45 g, 2.3 mmol, 0.7 equiv Pd), NaHCO3 (0.120 g, 1.43 mmol, 0.4 equiv), and MeOH (40 mL). H2 gas was then bubbled through the reaction mixture for 30 min, after which time the reaction contents were stirred at 25 °C under a H2 atmosphere (1 atm) for 2.5 h. Upon completion, the reaction mixture was filtered by vacuum filtration using filter paper (Whatman 1) and a Buchner funnel. The filtrate was concentrated, dissolved in MeOH (40 mL), and Amberlite (IR-120H, 4.00 g, pre-washed with MeOH five times) was added to the filtrate and the resultant mixture was warmed to 50 °C and stirred at that temperature for 1 h. Upon completion, the reaction contents were filtered by gravity filtration through filter paper (Whatman 1) and the resulting filtrate concentrated. Pressing forward, the resulting residue was dissolved in MeCN (50 mL) at 25 °C. To this solution was added chloromethyl methyl ether (2.60 mL, 33.5 mmol, 10 equiv) followed carefully by *i*Pr_2NEt (5.85 mL, 33.5 mmol, 10 equiv) and the resulting reaction mixture stirred for 12 h at 25 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (20 mL), poured into water (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) to give per-MOM protected silyl ether (0.916 g, 35% yield from **117**) as a pale yellow foam. Pressing forward, this newly synthesized material (0.916 g, 1.17 mmol, 1.0 equiv) was dissolved in THF (15 mL) and treated with *n*-Bu_4NF (2.34 mL, 1.0 M in THF, 2.34 mmol, 2.0 equiv) at 50 °C. After stirring the reaction contents at 50 °C for 12 h, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (10 mL), poured into water (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with brine (10 mL), dried

($MgSO_4$), concentrated, and purified by flash column chromatrography (silica gel, hexanes/EtOAc, 3:2) to give **154** (0.611 g, 96% yield) as a pale yellow foam. [Note: Solid NaHCO3 was used in the hydrogenation step to buffer the relatively high acidity of the palladium catalyst used. The progress of this hydrogenation varied heavily with different bottles of palladium catalyst and needed to be reinvestigated with each new commercial bottle.] **154**: R_f = 0.24 (silica gel, hexanes/EtOAc, 1:1); IR (film) ν_{max} 3483, 2903, 1593, 1511, 1441, 1402, 1287, 1261, 1234, 1213, 1146, 1129, 1076, 1019, 920, 833, 735, 697, 659, 616, 517; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2 H), 7.01 (d, *J* = 8.7 Hz, 2 H), 6.66 (t, *J* = 2.2 Hz, 1 H), 6.66 (d, *J* = 2.3 Hz, 1 H), 6.62 (d, *J* = 2.2 Hz, 1 H), 6.48 (d, *J* = 2.2 Hz, 2 H), 5.47 (d, *J* = 6.5 Hz, 1 H), 5.19 (s, 2 H), 5.17 (s, 2 H), 5.12 (d, *J* = 6.7 Hz, 2 H), 5.09 (d, *J* = 6.8 Hz, 2 H), 4.46 (d, *J* = 6.5 Hz, 1 H), 4.24 (s, 2 H), 3.51 (s, 3 H), 3.47 (s, 3 H), 3.45 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 159.1, 158.9, 157.3, 145.2, 138.9, 134.7, 127.1, 120.1, 116.5, 109.3, 108.3, 103.6, 97.9, 94.8, 94.6, 94.5, 93.2, 62.5, 56.5, 56.3, 56.3, 56.1; HRMS (FAB+) calcd for $C_{29}H_{34}O_{10}^+$ [M^+] 542.2152, found 542.2131.

Alkenes 156 and 157. Dess–Martin periodinane (0.560 g, 1.33 mmol, 1.2 equiv) was added in a single portion to a solution of alcohol **154** (0.600 g, 1.11 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) at 25 °C, and the resultant slurry was stirred for 1 h at 25 °C. Upon completion, the reaction contents were quenched by the addition of saturated aqueous Na_2SO_3 (5 mL) and stirred vigorously for 5 min at 25 °C. The reaction contents were then poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:1) to give the aldehyde (0.520 g, 87% yield) as a pale yellow foam. Pressing forward, KOt-Bu

(1.84 mL, 1.0 M in THF, 1.84 mmol, 3.9 equiv) was added dropwise over the course of 5 min to a solution of phosphonate **155** (0.911 g, 1.89 mmol, 4.0 equiv) in THF (8 mL) at –78 °C. After 20 min of stirring at –78 °C, a solution of the newly formed aldehyde (0.255 g, 0.47 mmol, 1.0 equiv) in THF (3 mL) was added at –78 °C. The resultant solution was stirred at –78 °C for 1 h, and then at 25 °C for 2 h. Subsequently, with *n*-Bu_4NF (12.6 mL, 1.0 M in THF, 12.6 mmol, 1.1 equiv) was added to the reaction mixture and allowed to stir for an addition 12 h at 25 °C. Upon completion, the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL), poured into water (5 mL), and extracted with EtOAc (3 x 15 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 85:15) to give **156** (0.156 g, 52% yield) and **157** (53.0 mg, 18% yield) as colorless foams.

***E*-ε-viniferin 158 and 159.** HCl (0.53 mL, 1.25 M in MeOH, 0.666 mmol, 30 equiv) was added to a solution of **156** (14.0 mg, 0.022 mmol, 1.0 equiv) in THF (0.5 mL) and stirred 25 °C for 4 h. Upon completion the reaction mixture was concentrated directly and purified by preparative TLC (CH_2Cl_2/MeOH, 4:1) to give *E*-ε-viniferin (**158**, 7.5 mg, 74% yield) as a colorless foam. **158**: R_f = 0.19 (silica gel, CH_2Cl_2/MeOH, 9:1); IR (film) ν_{max} 3310, 2945, 1708, 1602, 1513, 1449, 1372, 1339, 1266, 1168, 1122, 1057, 1002, 962, 832, 750, 710, 613, 577, 546, 514 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.20 (d, *J* = 8.5 Hz, 2 H), 7.17 (d, *J* = 8.6 Hz, 2 H), 6.91 (d, *J* = 16.4 Hz, 1 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 6.73 (d, *J* = 8.6 Hz, 2 H), 6.72 (d, *J* = 2.0 Hz, 1 H), 6.71 (d, *J* = 16.1 Hz, 1 H), 6.32 (d, *J* = 2.0 Hz, 1 H), 6.24 (s, 3 H), 5.42 (d, *J* = 5.4 Hz, 1 H), 4.47 (d, *J* = 5.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 159.9, 159.6, 158.2, 147.4,

136.4, 133.9, 130.9, 130.1, 129.9, 128.7, 127.9, 123.5, 119.8, 116.3, 116.2, 107.0, 104.2, 102.1, 96.8, 93.9, 57.1; HRMS (FAB+) calcd for $C_{28}H_{22}O_6^+$ [M^+] 454.1416, found 454.1426.

***Z*-ε-viniferin 159.** HCl (1.21 mL, 1.25 M in MeOH, 1.51 mmol, 50 equiv) was added to a solution of **157** (19.0 mg, 0.030 mmol, 1.0 equiv) in THF (1.2 mL) and stirred 25 °C for 2.5 h. Upon completion the reaction mixture was concentrated directly and purified by preparative TLC (CH_2Cl_2/MeOH, 4:1) to give *Z*-ε-viniferin (**159**, 11.5 mg, 84% yield) as a colorless foam. **159**: R_f = 0.19 (silica gel, CH_2Cl_2/MeOH, 9:1); IR (film) ν_{max} 3292, 1596, 1512, 1441, 1338, 1238, 1156, 1120, 1000, 866, 831, 753, 691, 668, 624, 587, 554, 514; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.06 (d, *J* = 8.6 Hz, 2 H), 7.01 (d, *J* = 8.6 Hz, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 6.66 (d, *J* = 8.6 Hz, 2 H), 6.30 (d, *J* = 1.8 Hz, 1 H), 6.29 (d, *J* = 2.1 Hz, 1 H), 6.23 (d, *J* = 12.1 Hz, 1 H), 6.20 (t, *J* = 2.2 Hz, 1 H), 6.04 (d, *J* = 2.2 Hz, 2 H), 6.03 (d, *J* = 12.4 Hz, 1 H), 5.28 (d, *J* = 5.5 Hz, 1 H), 3.99 (d, *J* = 5.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 159.6, 159.4, 158.2, 157.7, 147.1, 137.1, 133.8, 131.2, 130.9, 129.4, 128.2, 126.2, 120.1, 116.1, 115.8, 108.5, 106.9, 101.9, 96.6, 94.1, 57.0; HRMS (FAB+) calcd for $C_{28}H_{22}O_6^+$ [M^+] 454.1416, found 454.1430.

Figure 3. Additional Compounds.

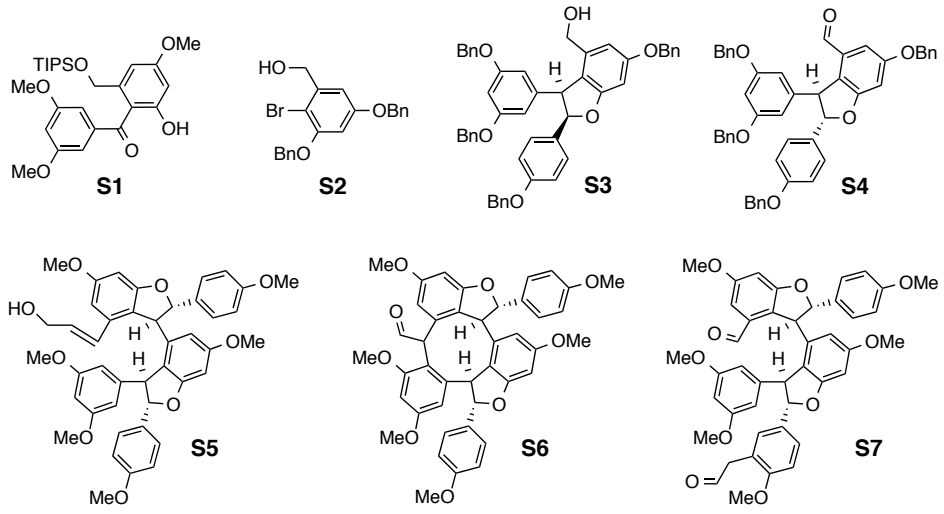
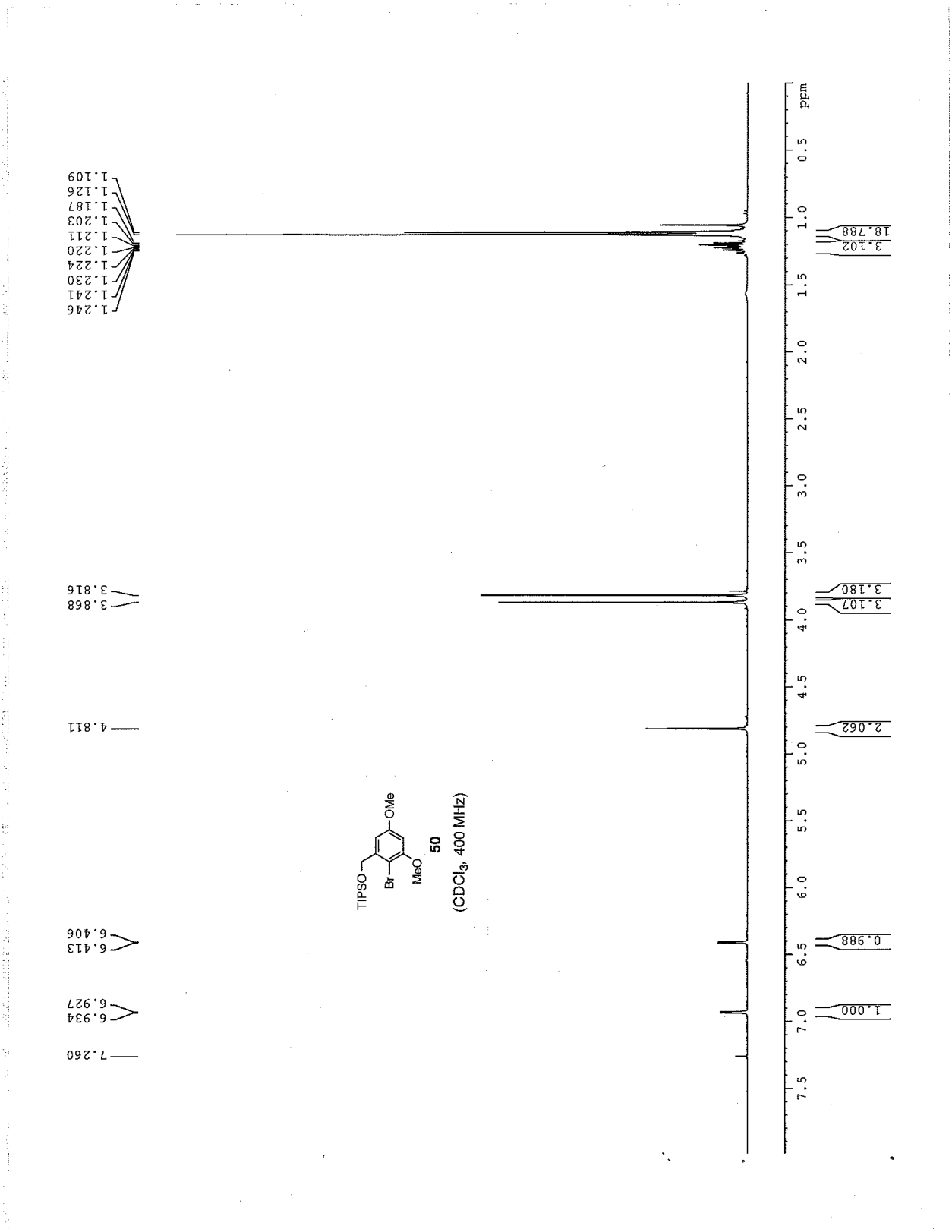


Table 1. Spectral Comparison of Caraphenol A (**1**)

^{1}H NMR in acetone-d_6	
Natural Caraphenol A	**Synthetic Caraphenol A**
7.26 (d, J = 8.7 Hz, 2 H)	7.25 (d, J = 8.7 Hz, 2 H)
7.24 (d, J = 8.6 Hz, 2 H)	7.23 (d, J = 8.4 Hz, 2 H)
7.05 (d, J = 8.6 Hz, 2 H)	7.05 (d, J = 8.6 Hz, 2 H)
6.94 (d, J = 1.8 Hz, 1 H)	6.92 (d, J = 1.9 Hz, 1 H)
6.81 (d, J = 1.8 Hz, 1 H)	6.79 (d, J = 1.9 Hz, 1 H)
6.80 (d, J = 8.7 Hz, 2 H)	6.79 (d, J = 8.6 Hz, 2 H)
6.75 (d, J = 8.6 Hz, 2 H)	6.75 (d, J = 8.8 Hz, 2 H)
6.71 (d, J = 8.6 Hz, 2 H)	6.69 (d, J = 8.6 Hz, 2 H)
6.54 (d, J = 1.8 Hz, 1 H)	6.53 (d, J = 2.0 Hz, 1 H)
6.52 (d, J = 2.1 Hz, 1 H)	6.49 (d, J = 2.0 Hz, 1 H)
6.32 (d, J = 2.1 Hz, 1 H)	6.31 (d, J = 2.2 Hz, 1 H)
6.25 (d, J = 1.8 Hz, 1 H)	6.24 (d, J = 2.0 Hz, 1 H)
5.92 (s, 1 H)	5.91 (s, 2 H)
5.91 (s, 1 H)	
4.87 (s, 1 H)	4.85 (s, 1 H)
4.31 (s, 1 H)	4.33 (s, 1 H)
^{13}C NMR in acetone-d_6	
45.71	46.04
54.06	54.04
87.92	88.02
95.17	95.18
96.36	96.41
97.64	97.58
98.32	98.45
108.71	108.70
108.75	108.72
109.65	109.74
114.50	114.57
115.85	115.83
116.01	116.03
116.18	116.18
118.93	119.19
120.56	120.73
122.71	122.95
122.79	122.96
127.37	127.45
128.15	128.31
128.34	128.34
132.49	132.84
133.51	133.71

135.32	135.35
139.67	139.8
140.95	141.09
149.27	149.62
155.22	155.3
157.20	157.08
158.02	157.97
158.21	158.07
158.29	158.17
159.17	159.10
159.79	159.99
160.72	160.56
163.49	163.60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1.211
1.220
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1.246
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6.406
6.413
6.927
6.934
7.260
TIPSO
Br
MeO
OMe
50
(CDCl3, 400 MHz)
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
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7.0
7.5
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3.180
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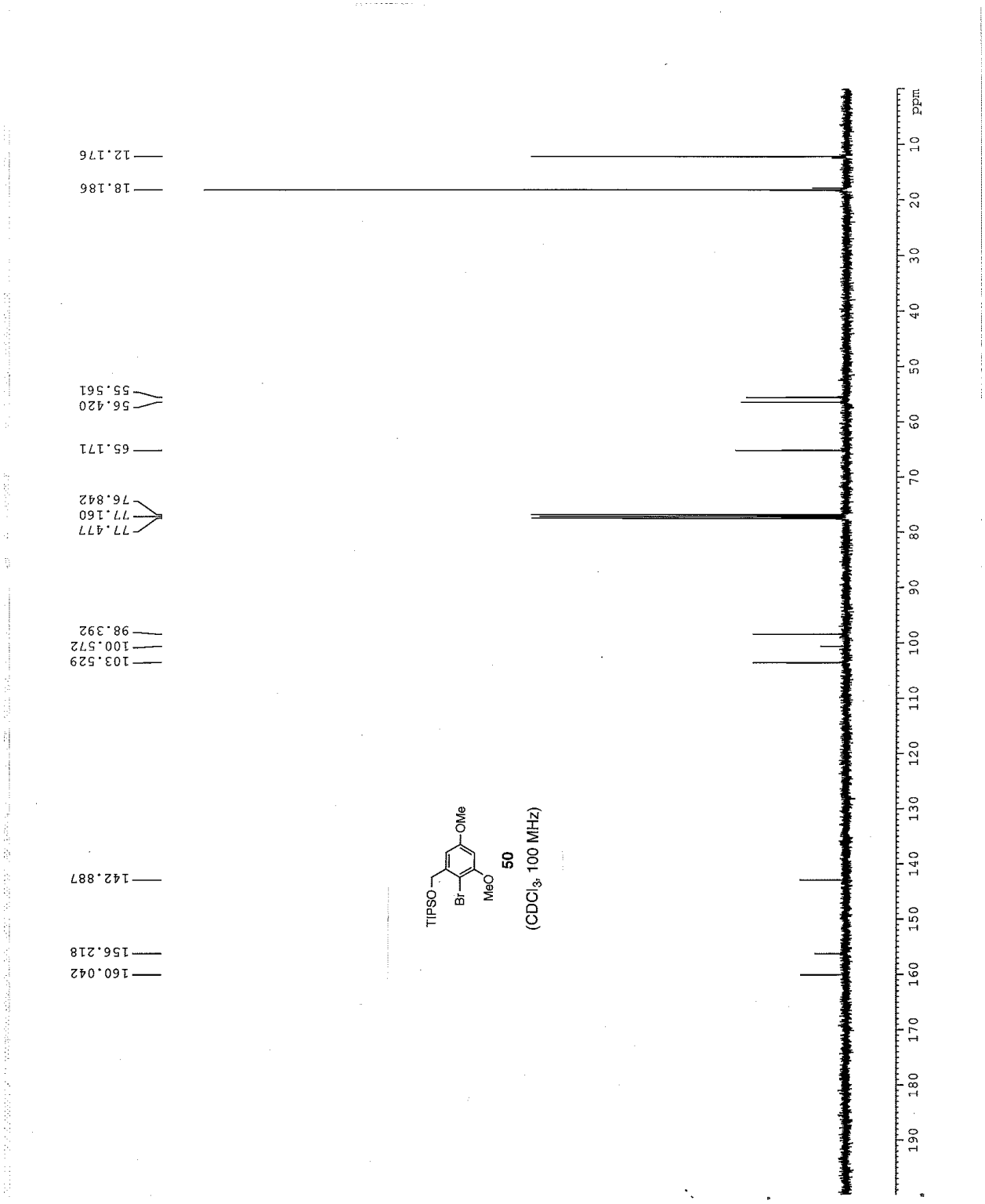
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65.171
76.842
77.160
77.477
98.392
100.572
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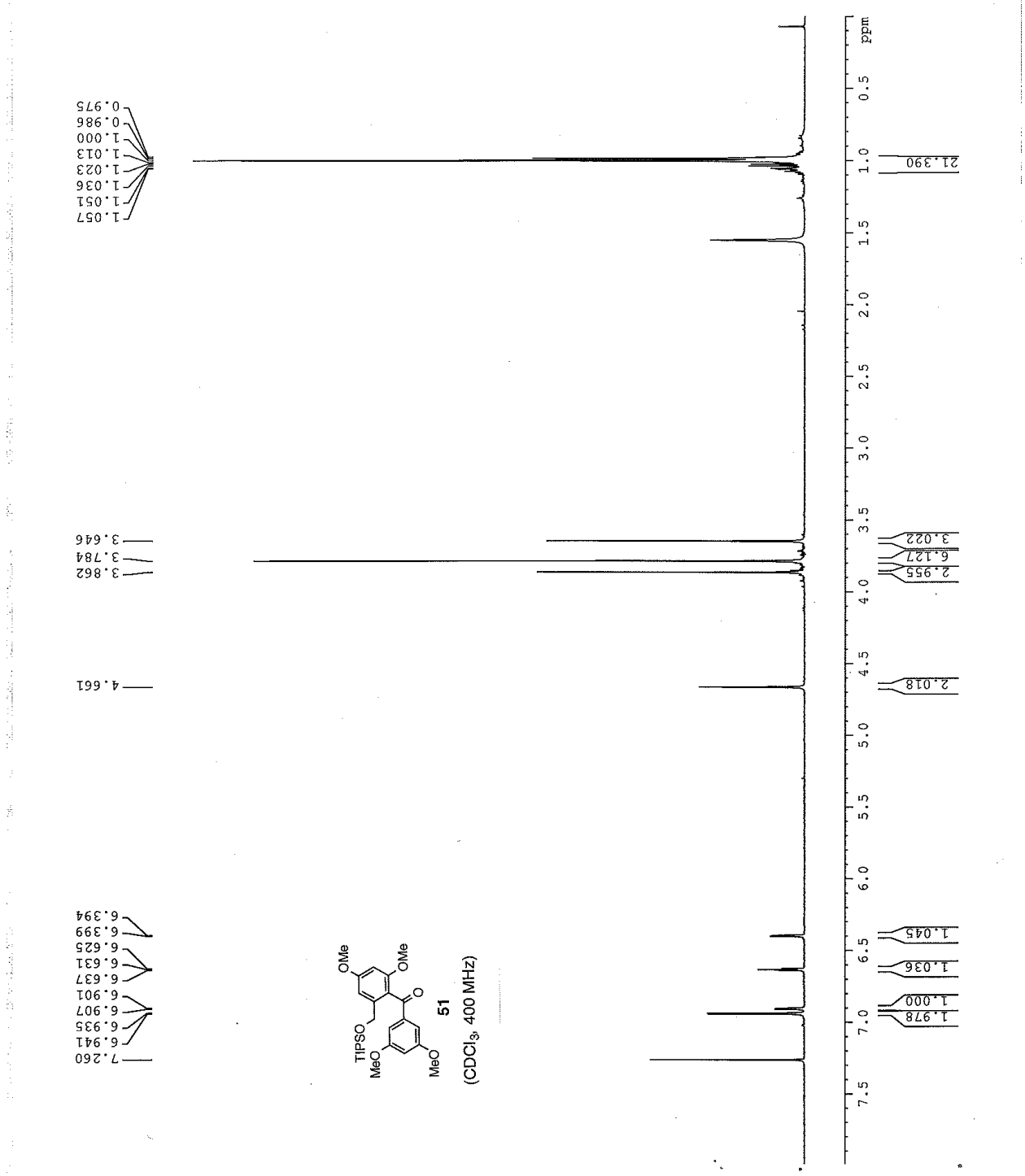
156.218
160.042
TIPSO
Br
MeO
OMe
50
(CDCl3, 100 MHz)
ppm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6.399
6.625
6.631
6.637
6.901
6.907
6.935
6.941
7.260
OMe
OMe
TIPSO
MeO
MeO
O
51
(CDCl3, 400 MHz)
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
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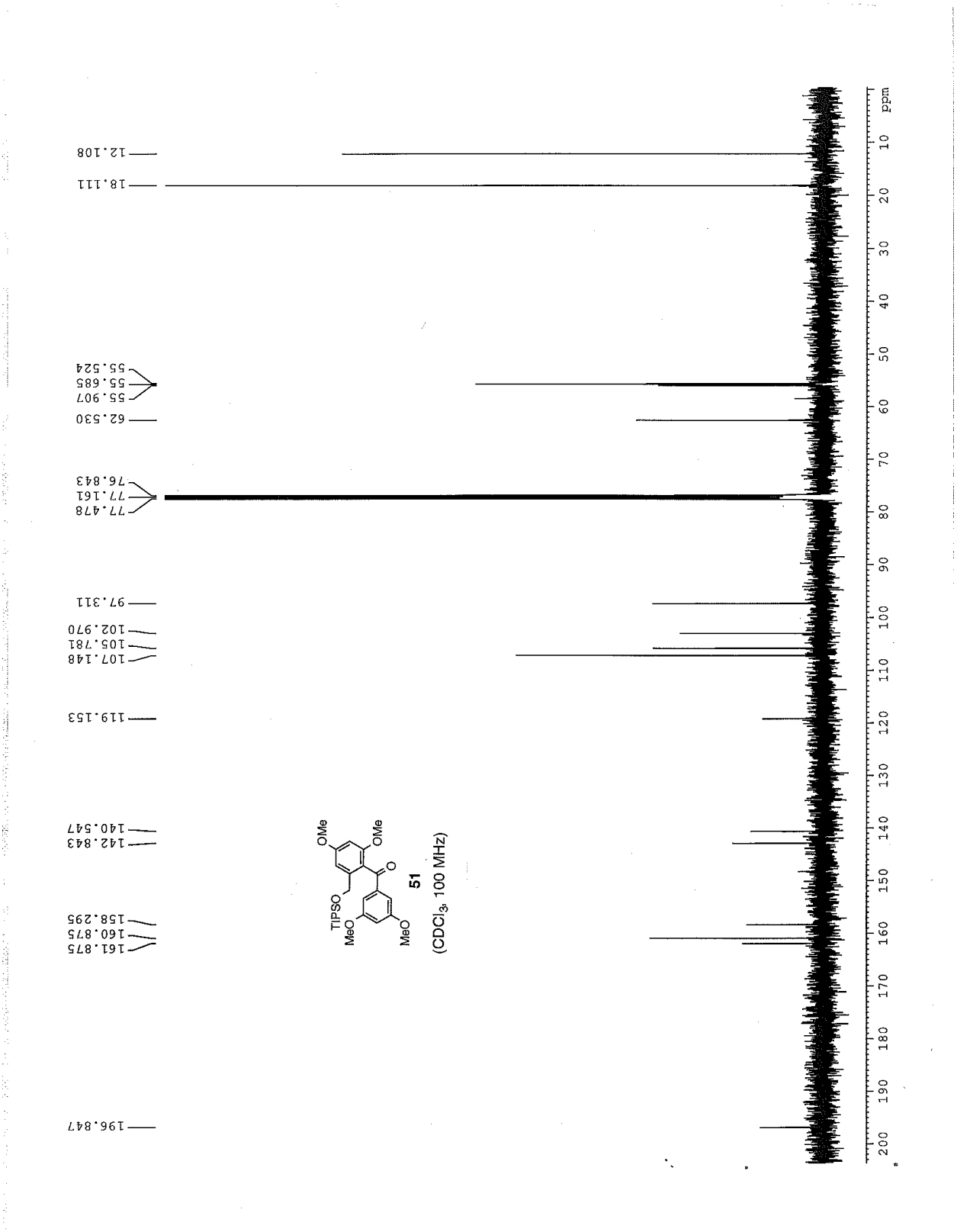
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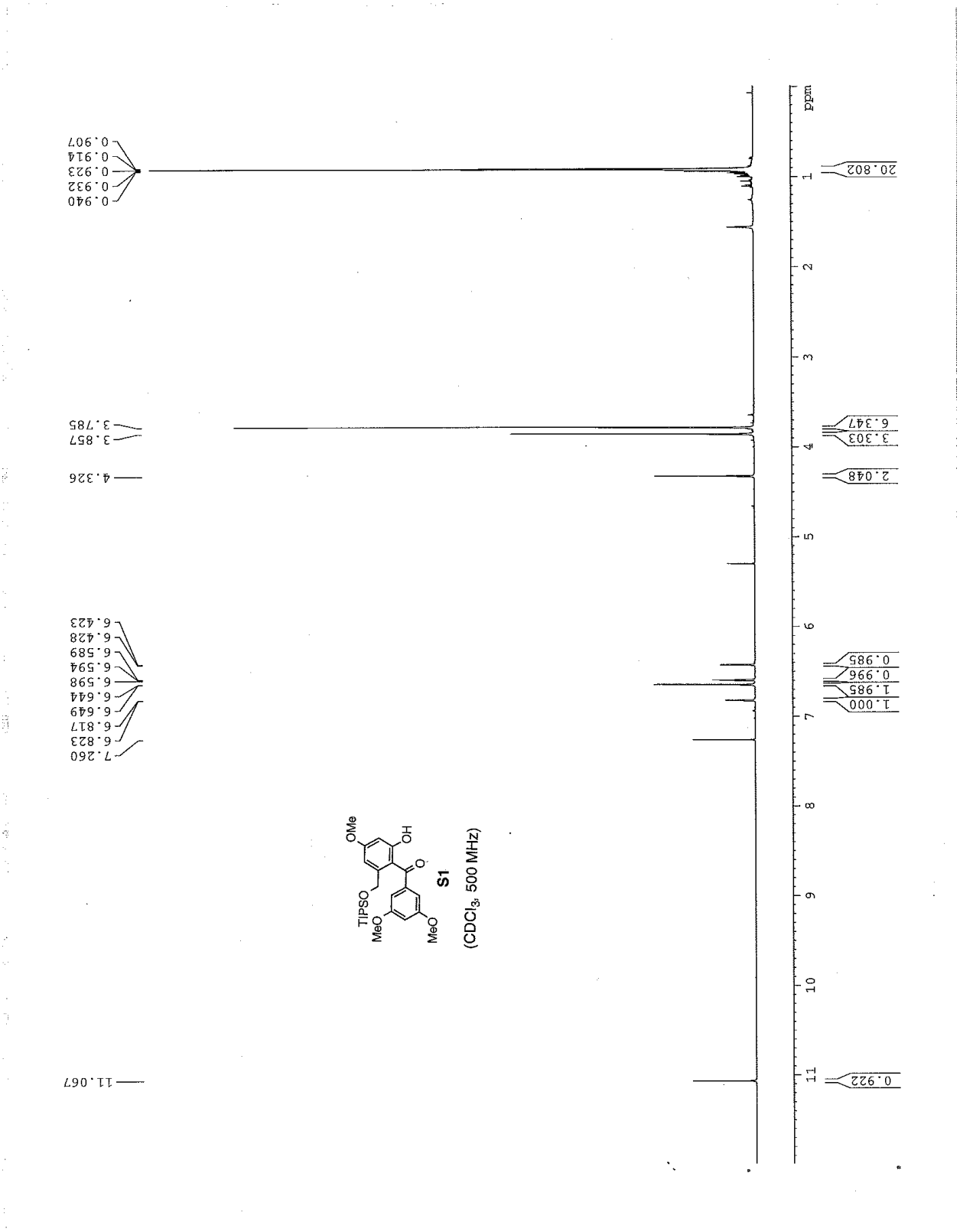
119.153
140.547
142.843
158.295
160.875
161.875
196.847
ppm
OMe
OMe
TIPSO
MeO
MeO
O
51
(CDCl3, 100 MHz)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6.644
6.649
6.817
6.823
7.260
11.067
20.802
6.347
3.303
2.048
0.985
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OH
O
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MeO
MeO
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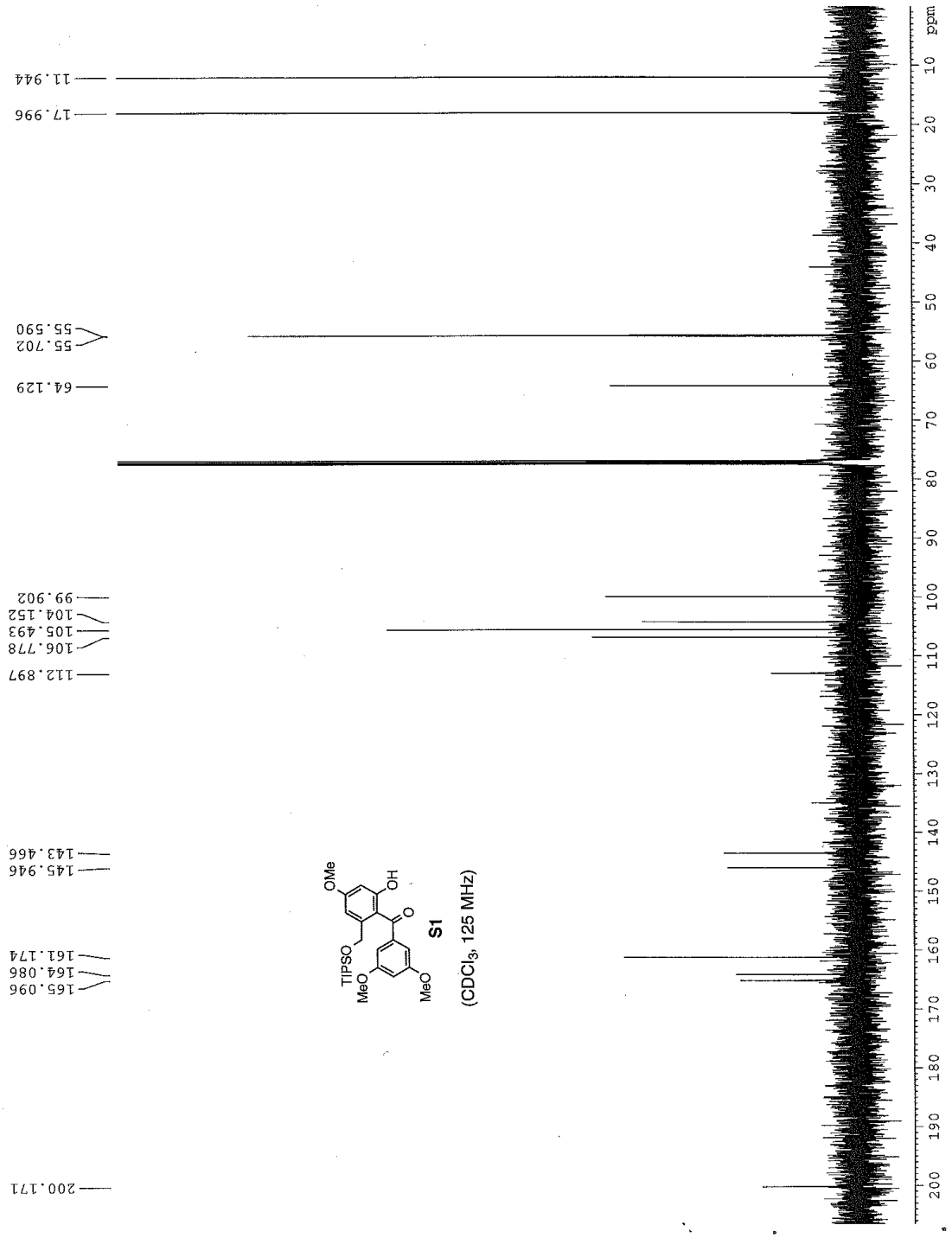
(CDCl3, 500 MHz)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ppm
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OH
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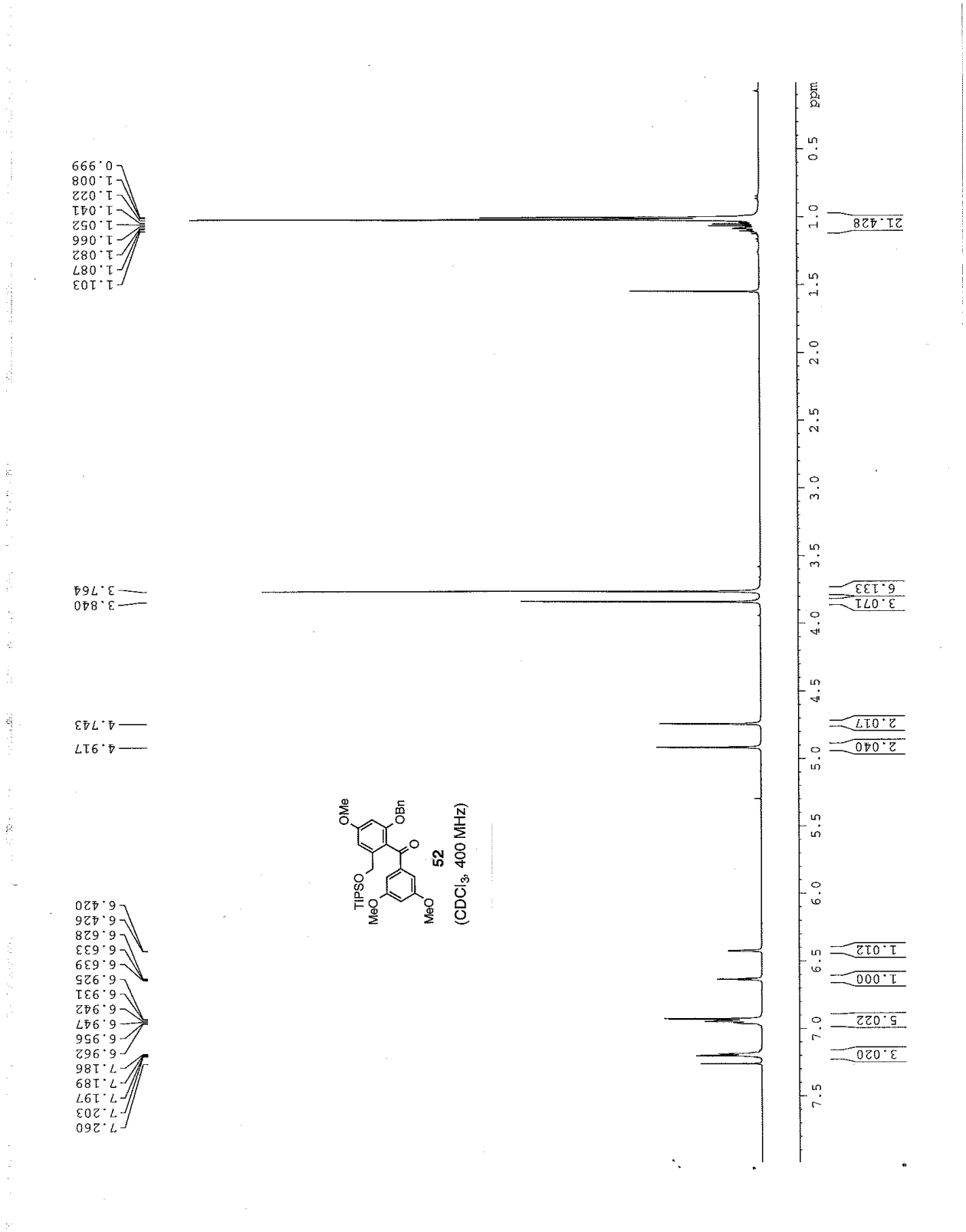
MeO
MeO
S1
(CDCl3, 125 MHz)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MeO
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1.022
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1.066
1.082
1.087
1.103
3.764
3.840
4.743
4.917
6.420
6.426
6.628
6.633
6.639
6.925
6.931
6.942
6.947
6.956
6.962
7.186
7.189
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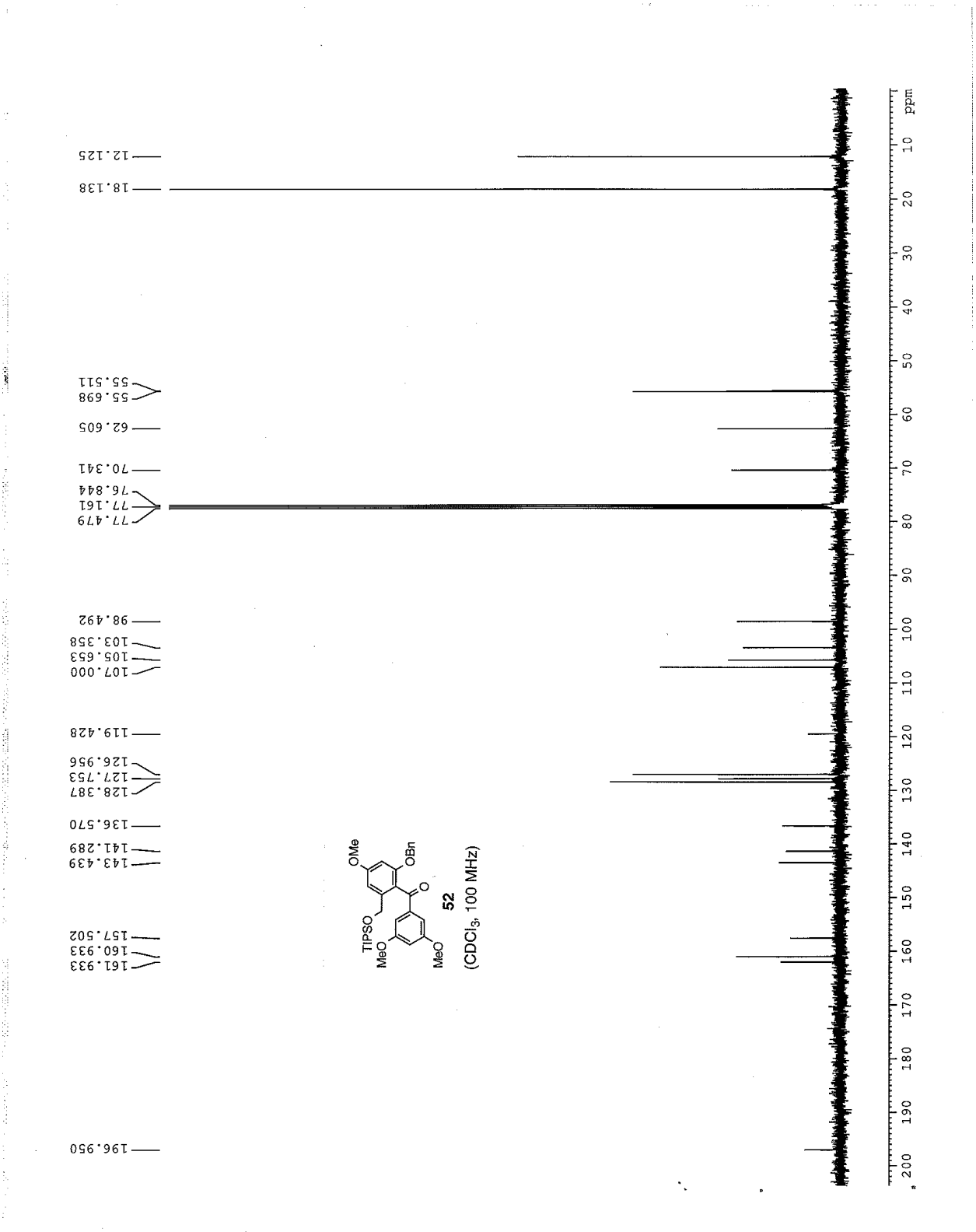
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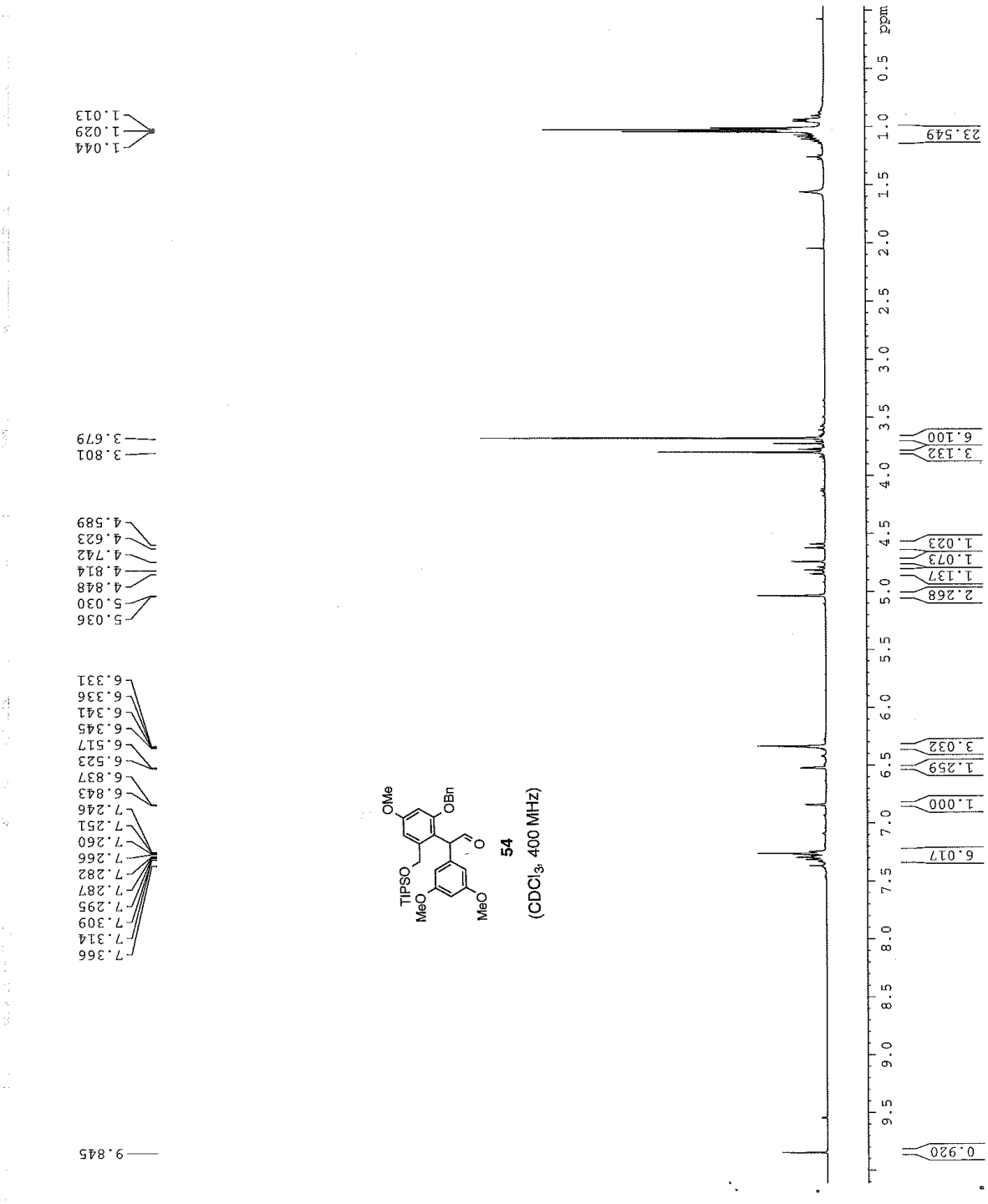
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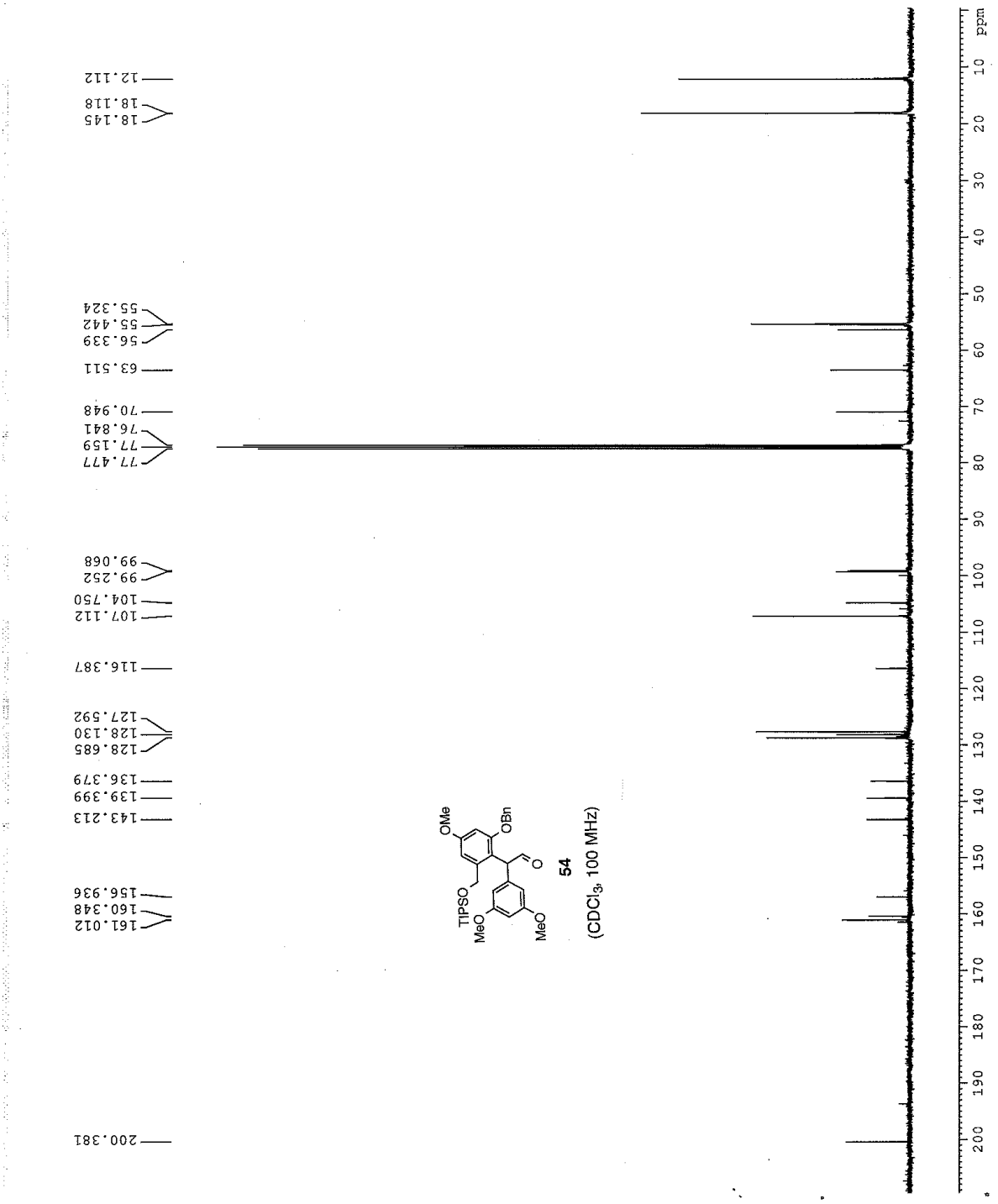
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128.130
128.685
136.379
139.399
143.213
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MeO
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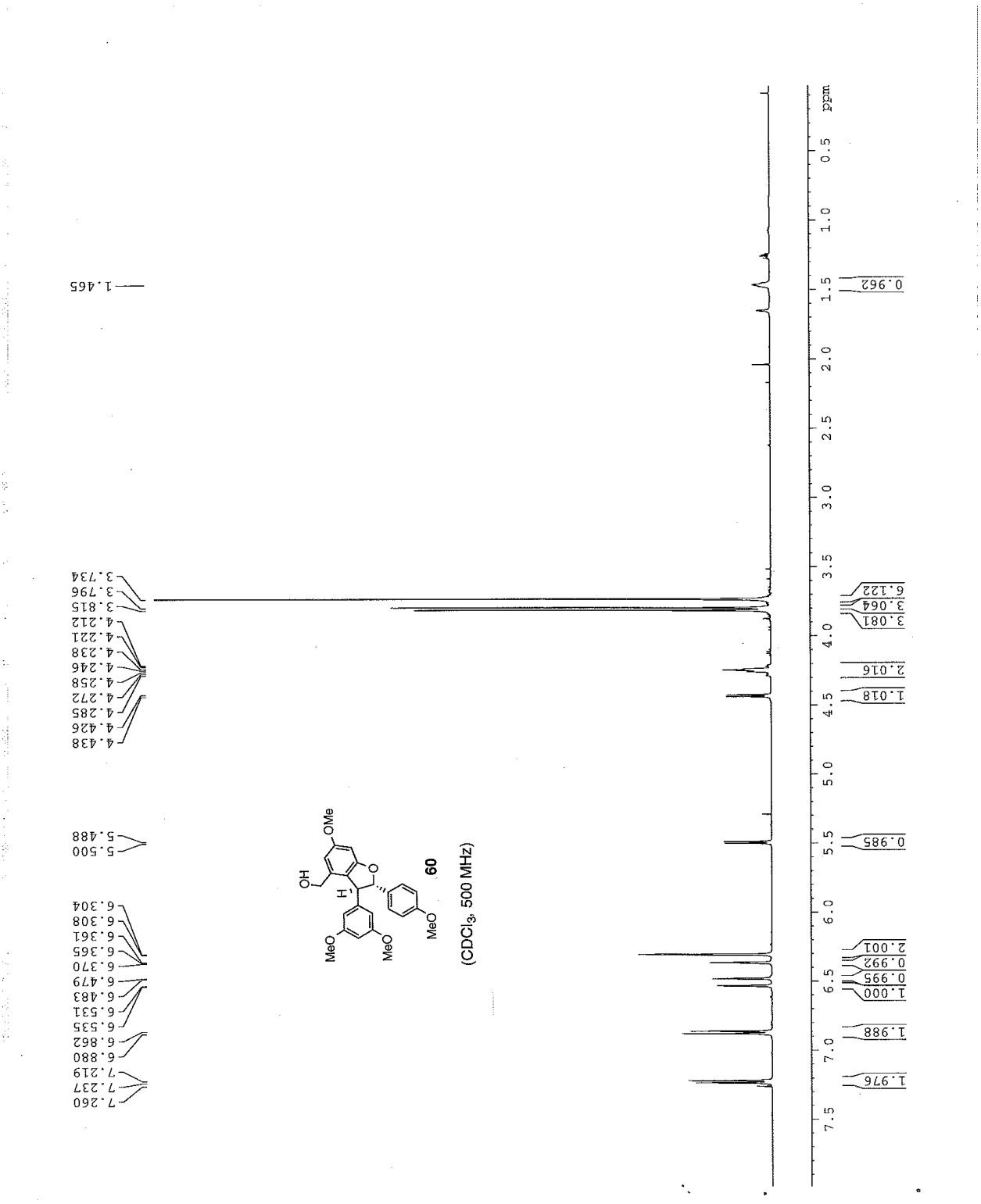
(CDCl3, 100 MHz)
ppm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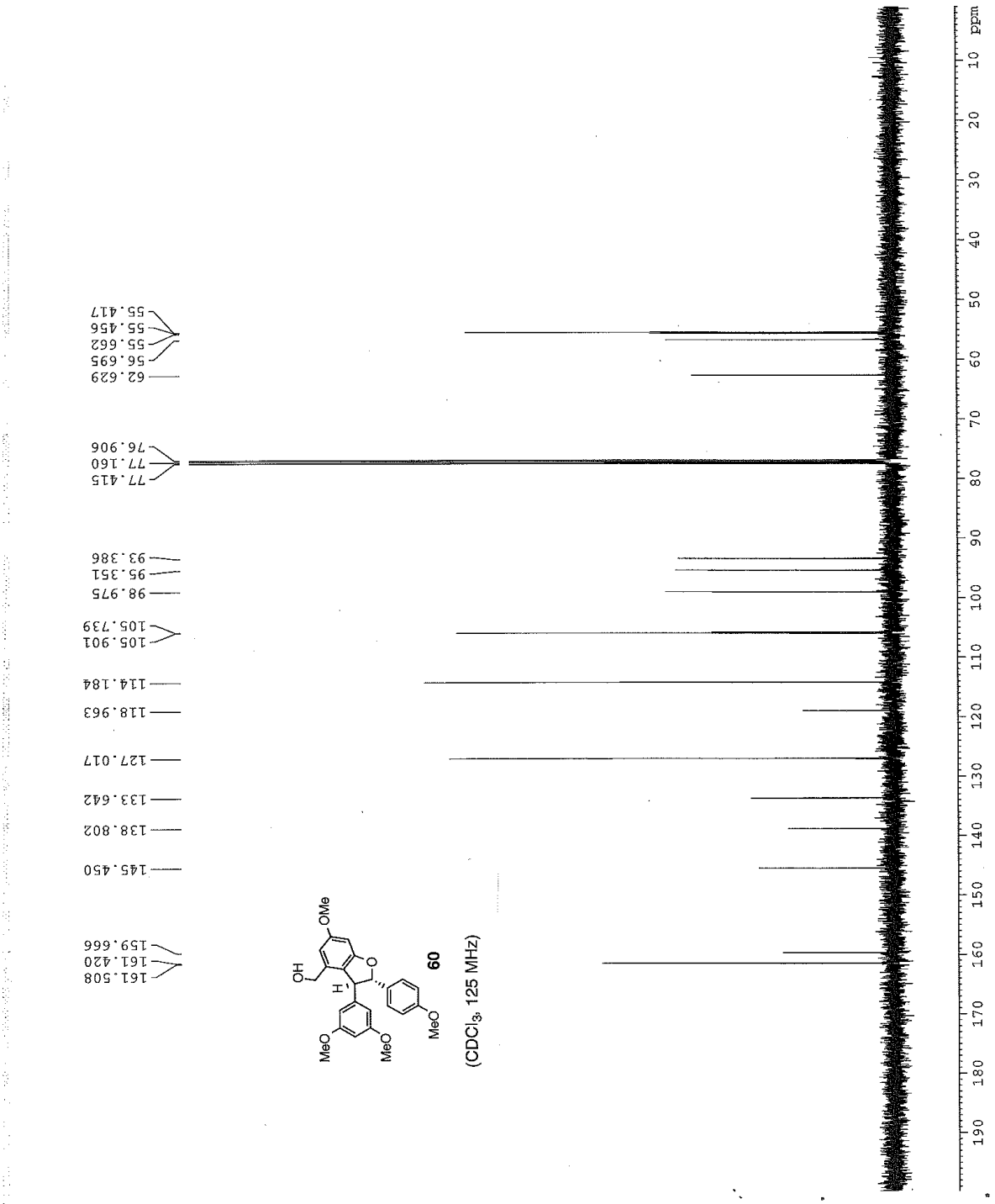
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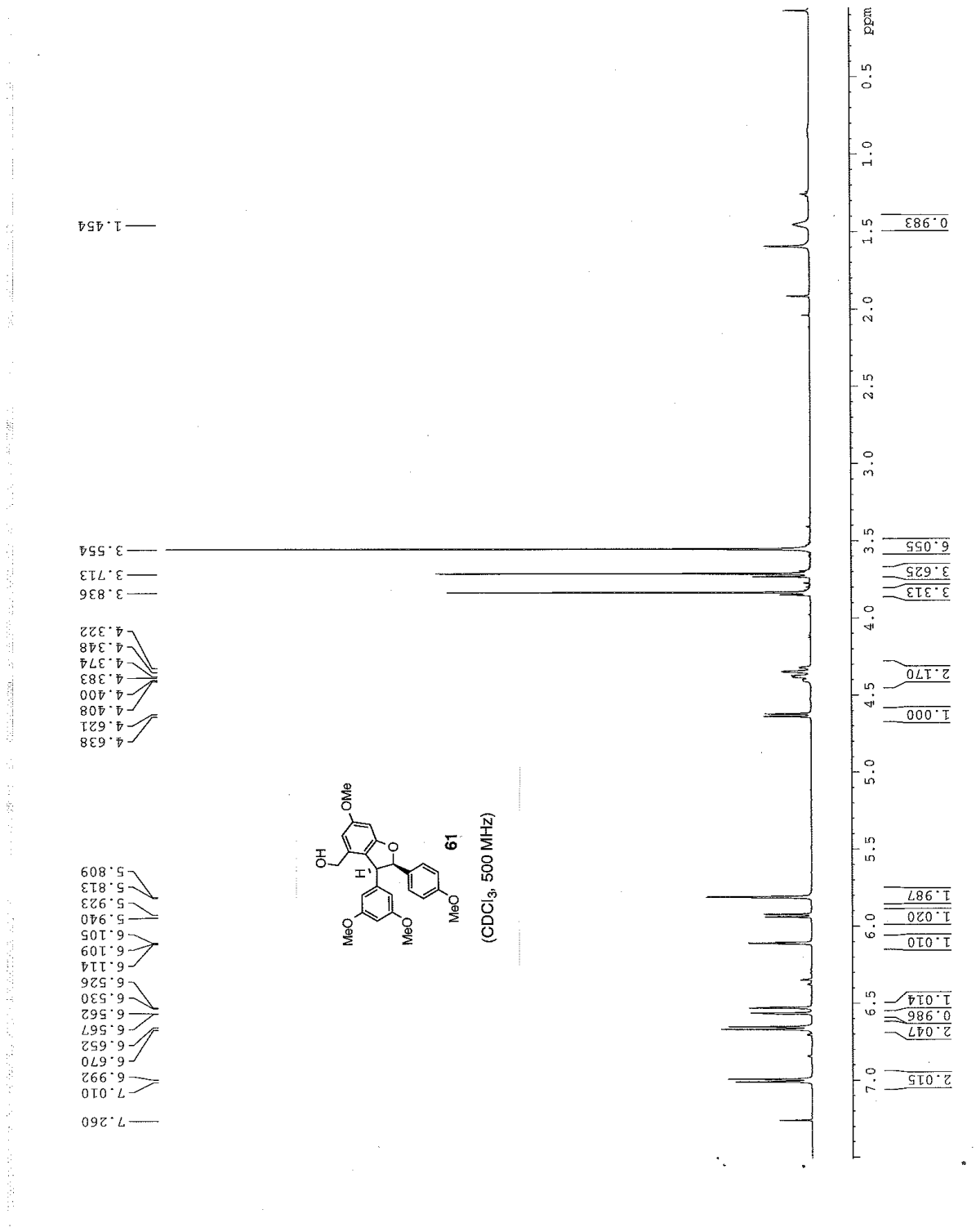
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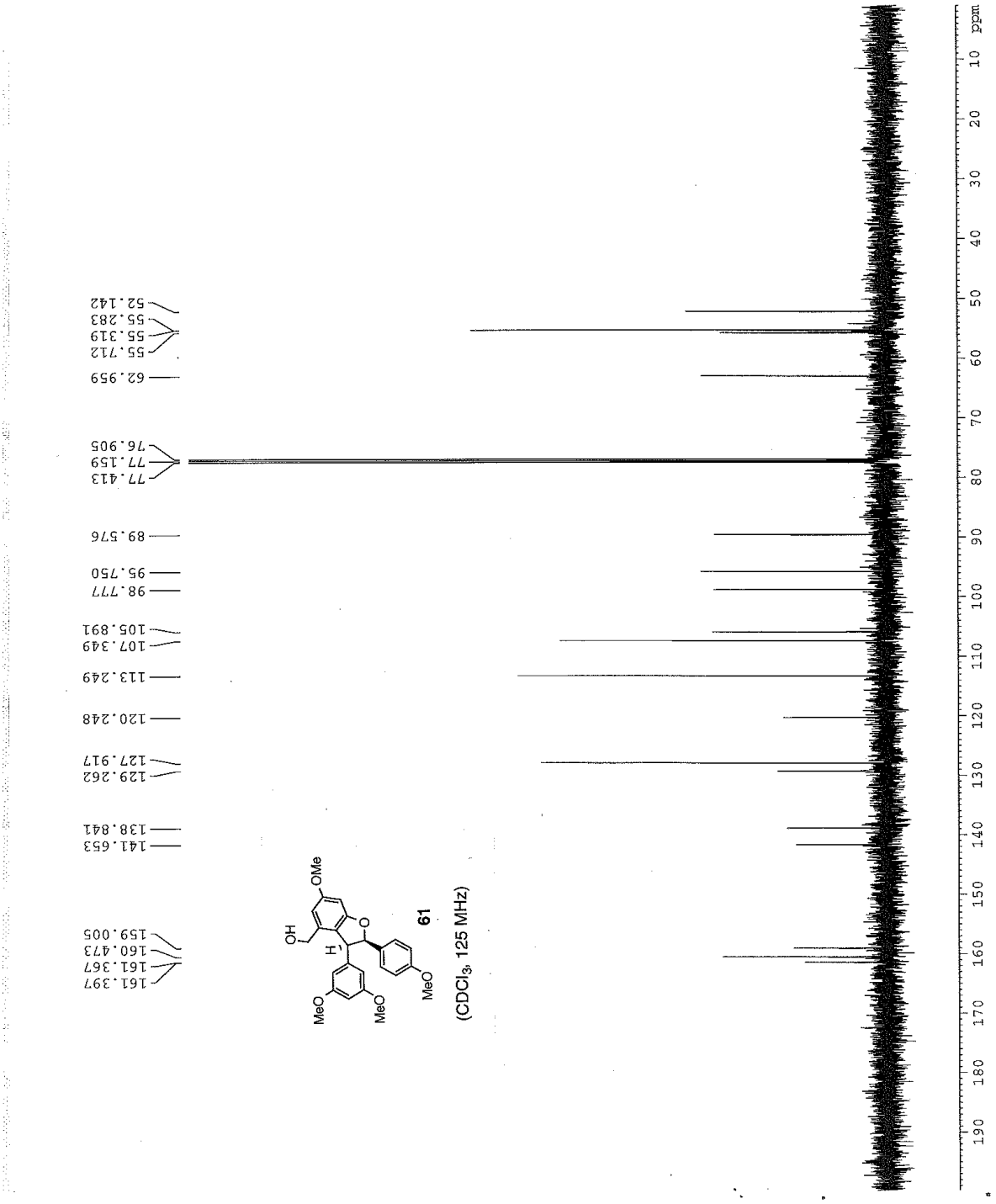
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MeO
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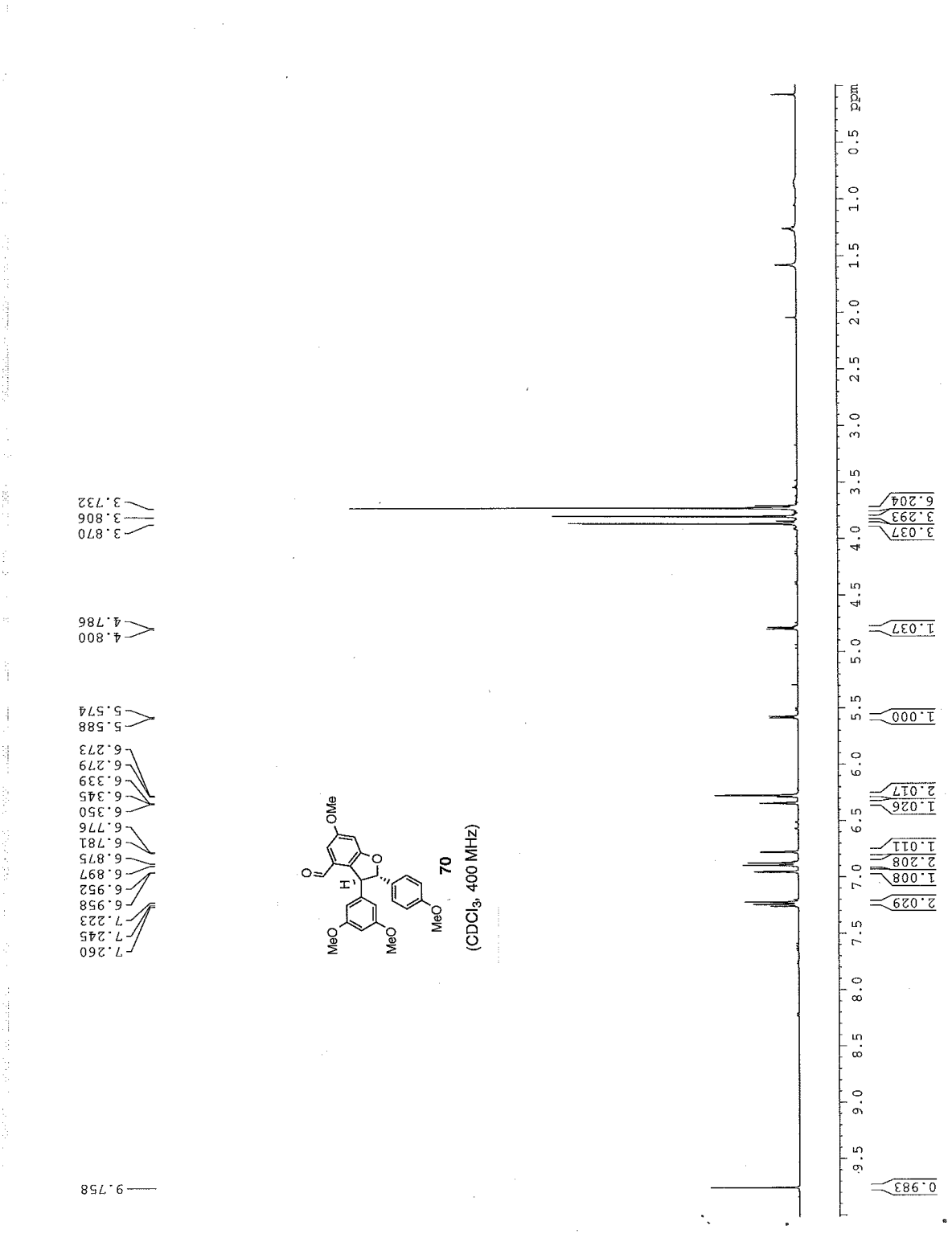
(CDCl3, 125 MHz)
ppm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OMe
O
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MeO
MeO
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(CDCl3, 400 MHz)
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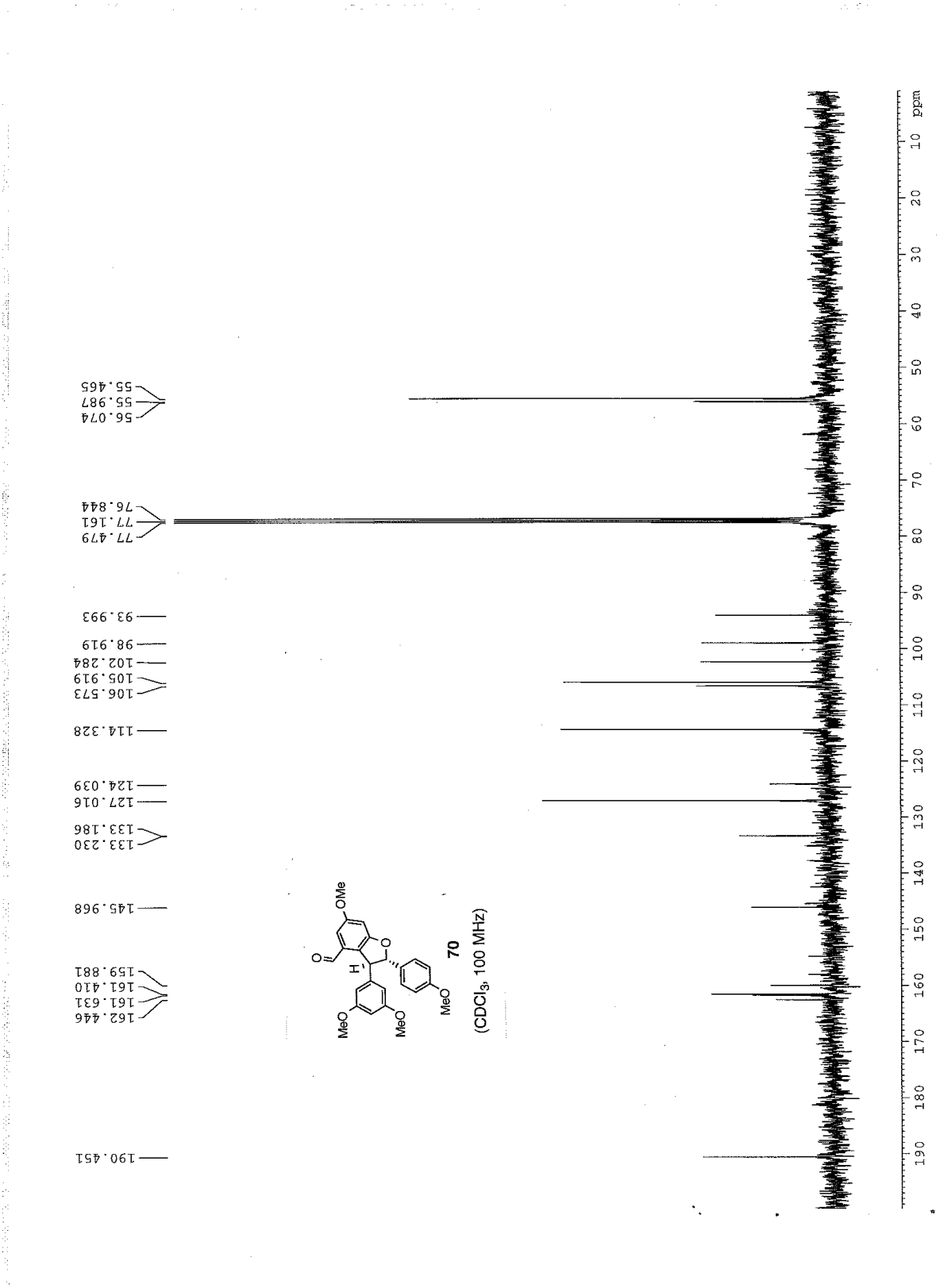
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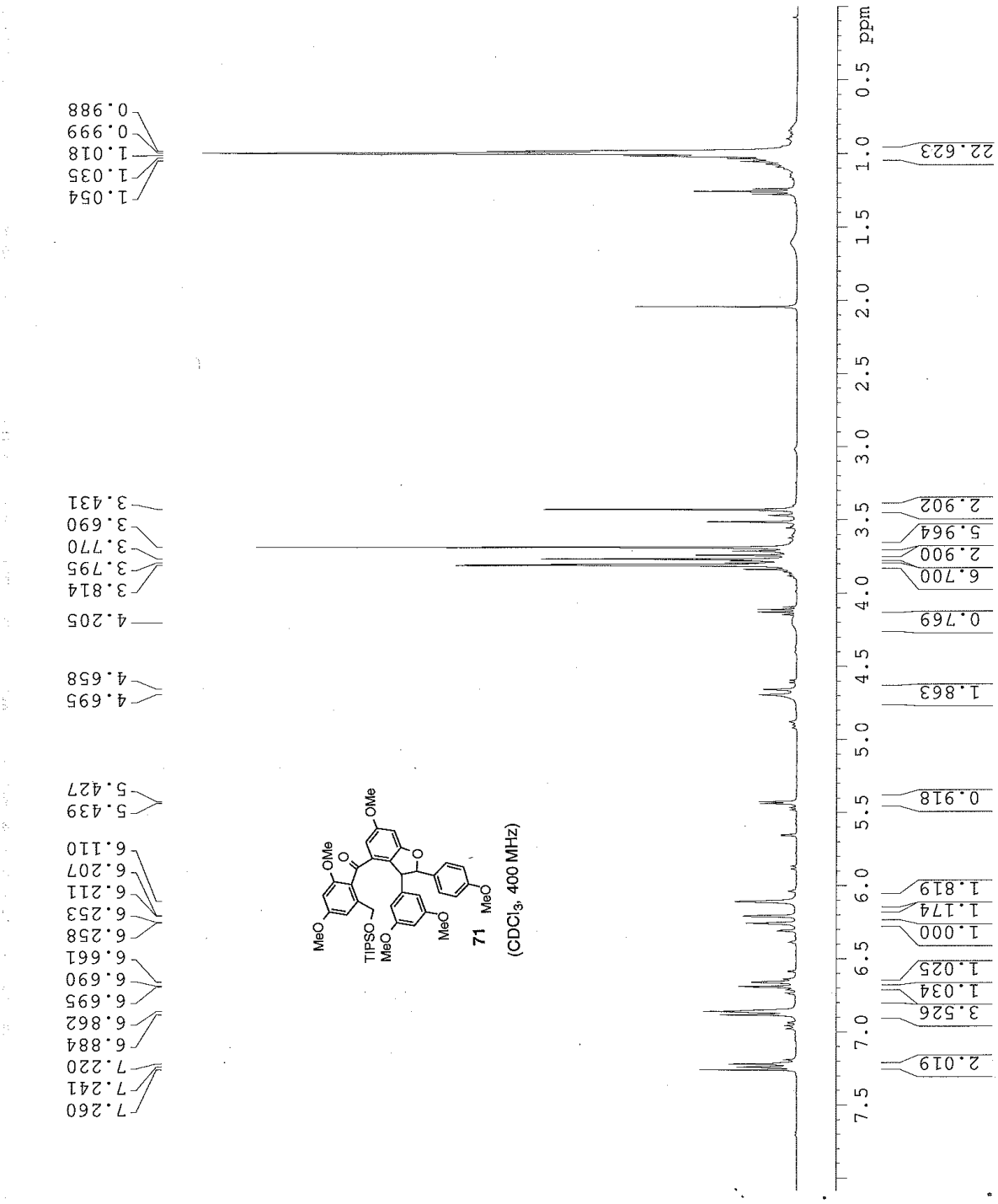
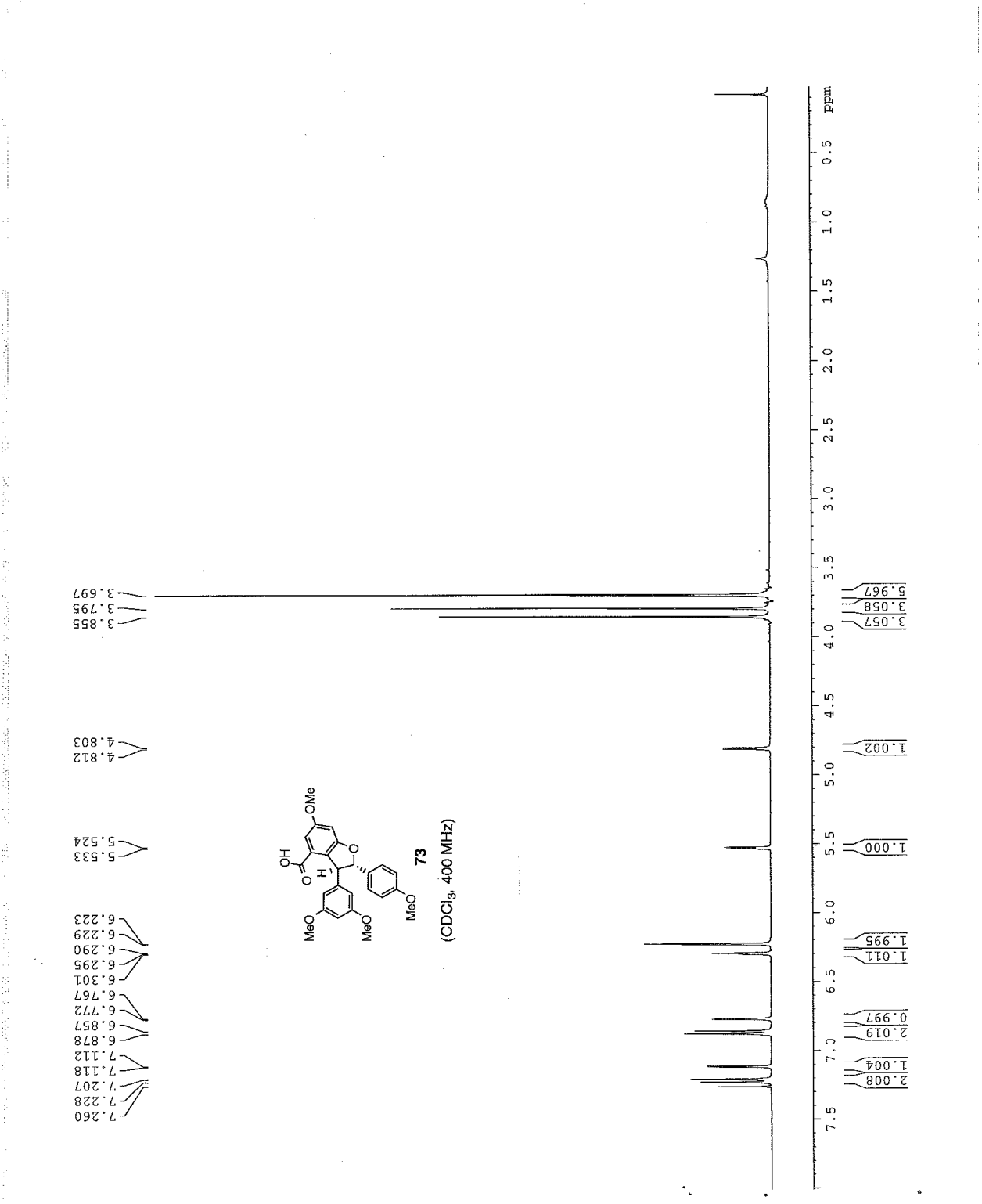
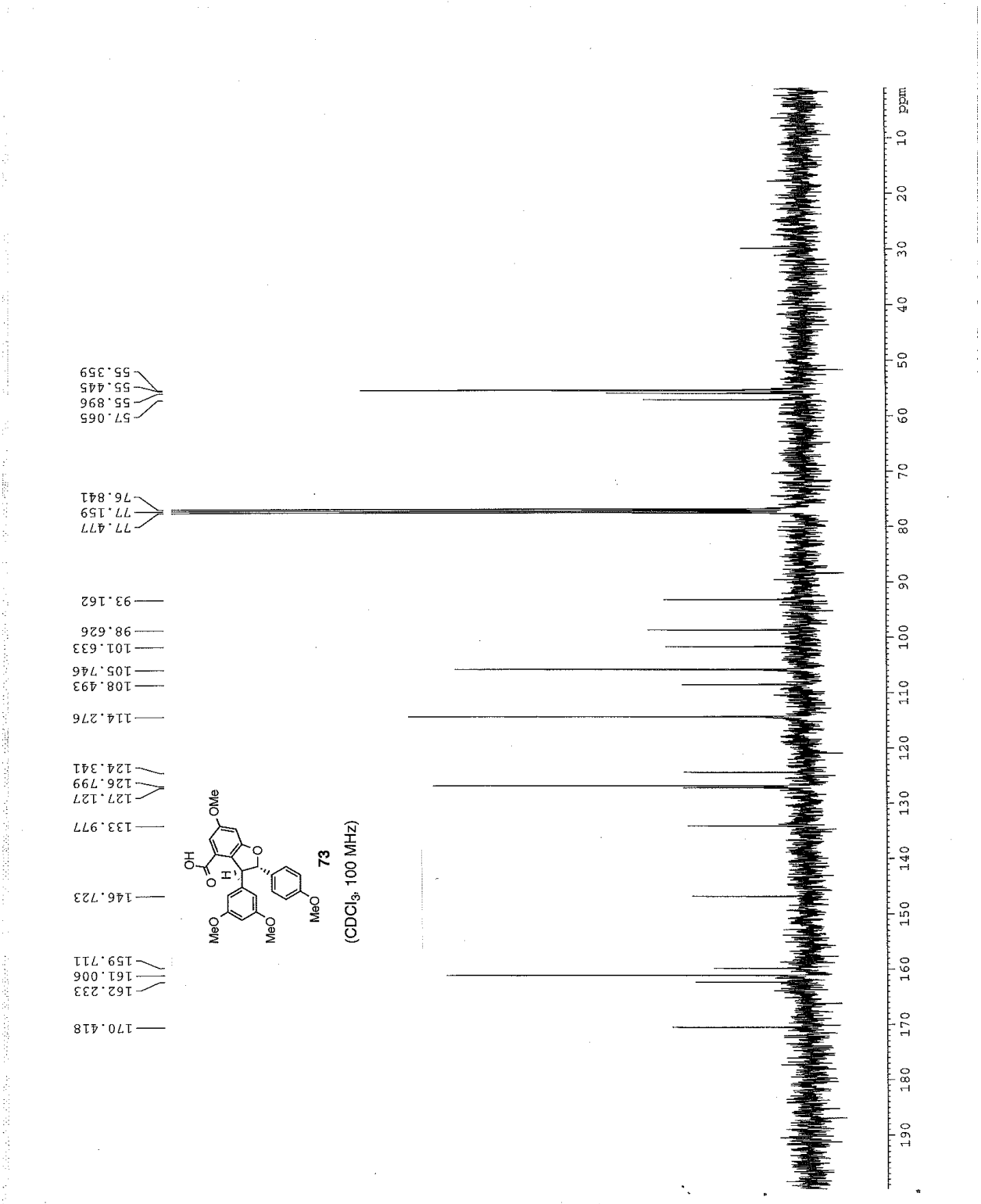
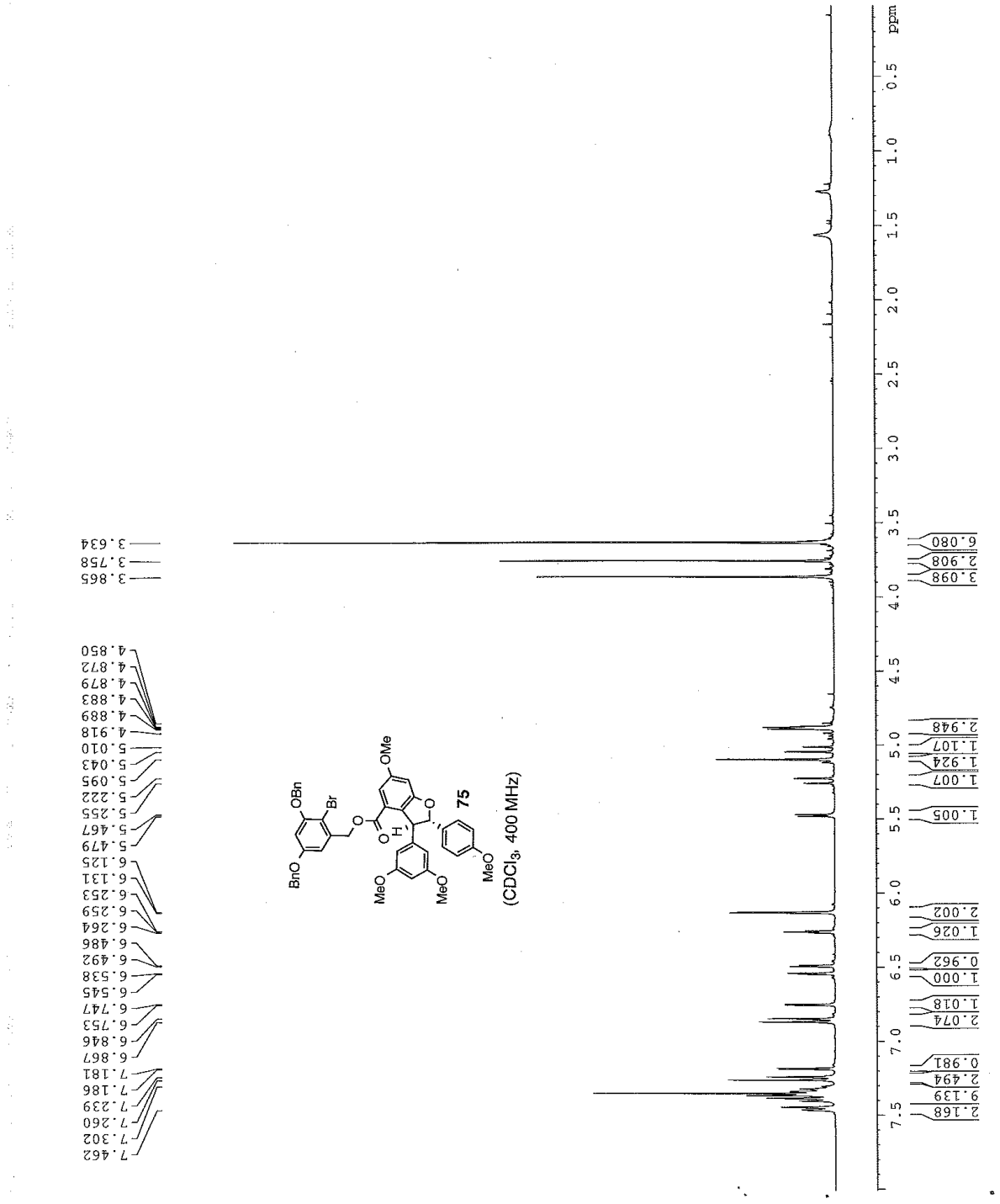
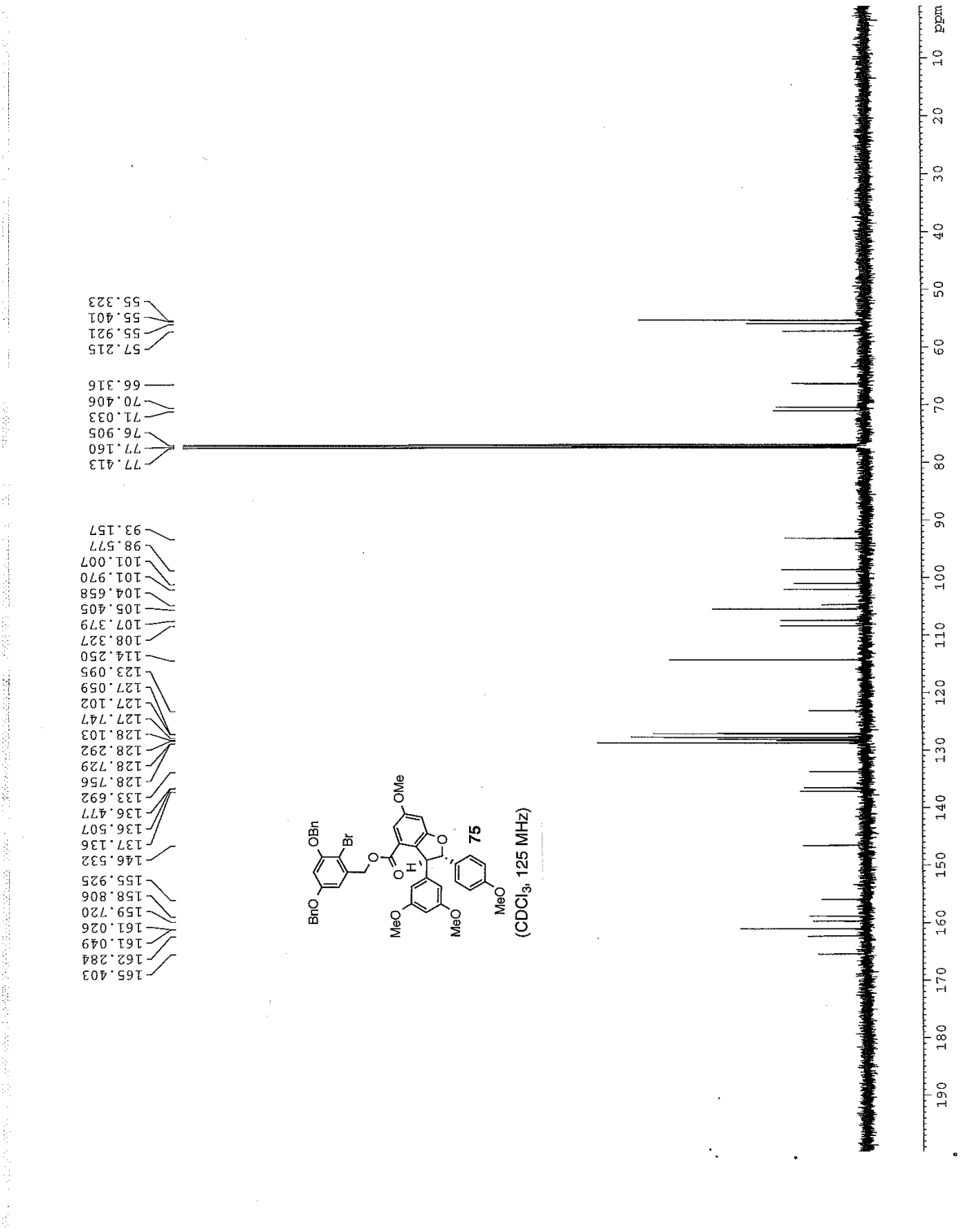
133.186
127.016
124.039
114.328
106.573
105.919
102.284
98.919
93.993
77.479
77.161
76.844
56.074
55.987
55.465
OMe
O
H
MeO
MeO
MeO
70
(CDCl3, 100 MHz)
ppm

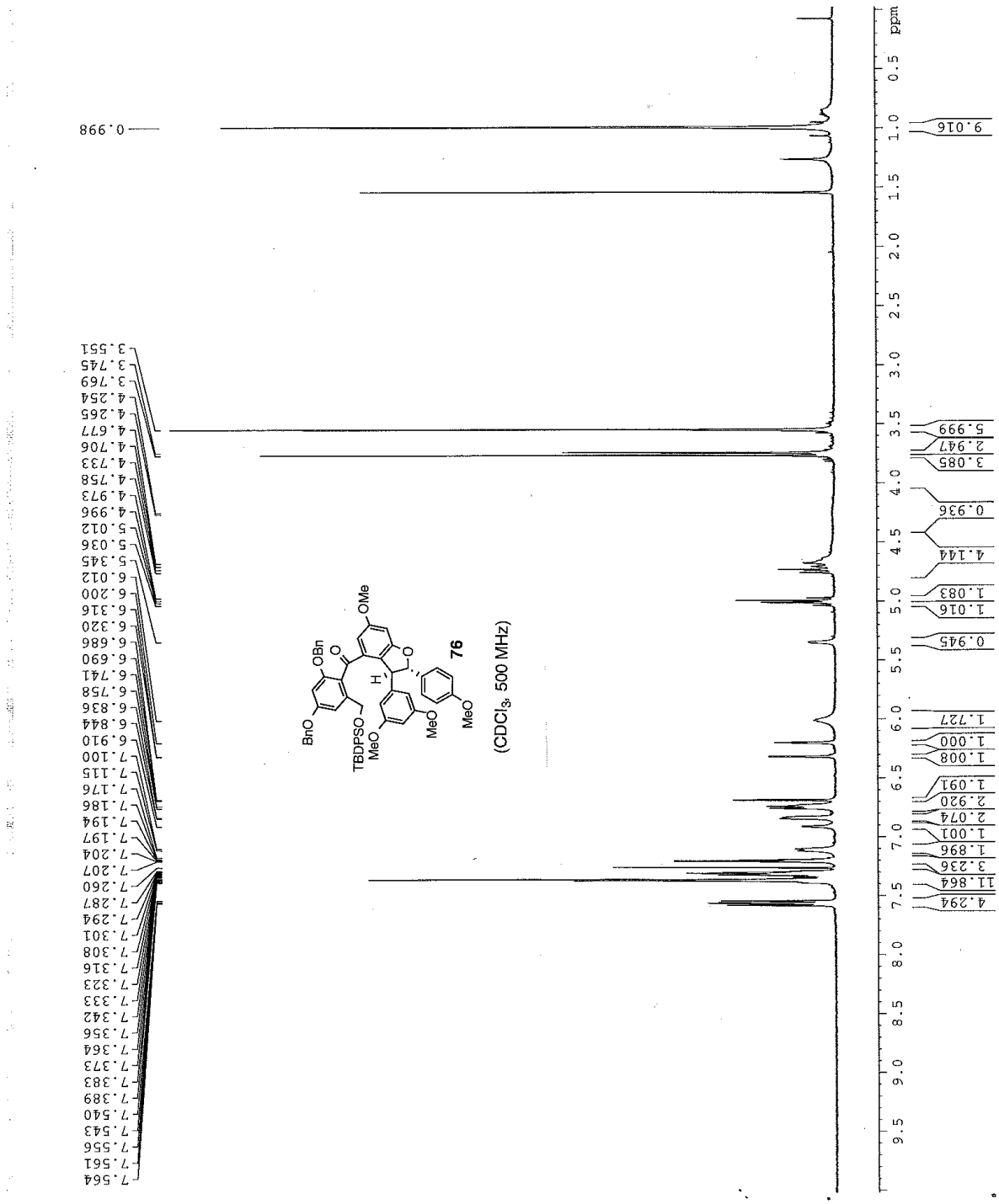

7.260
7.241
7.220
6.884
6.862
6.695
6.690
6.661
6.258
6.253
6.211
6.207
6.110
5.439
5.427
4.695
4.658
4.205
3.814
3.795
3.770
3.690
3.431
1.054
1.035
1.018
0.999
0.988
MeO
OMe
TIPSO
MeO
MeO
MeO
OMe
71
(CDCl3, 400 MHz)
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
2.019
3.526
1.034
1.025
1.000
1.174
1.819
0.918
1.863
0.769
6.700
2.900
5.964
2.902
22.623

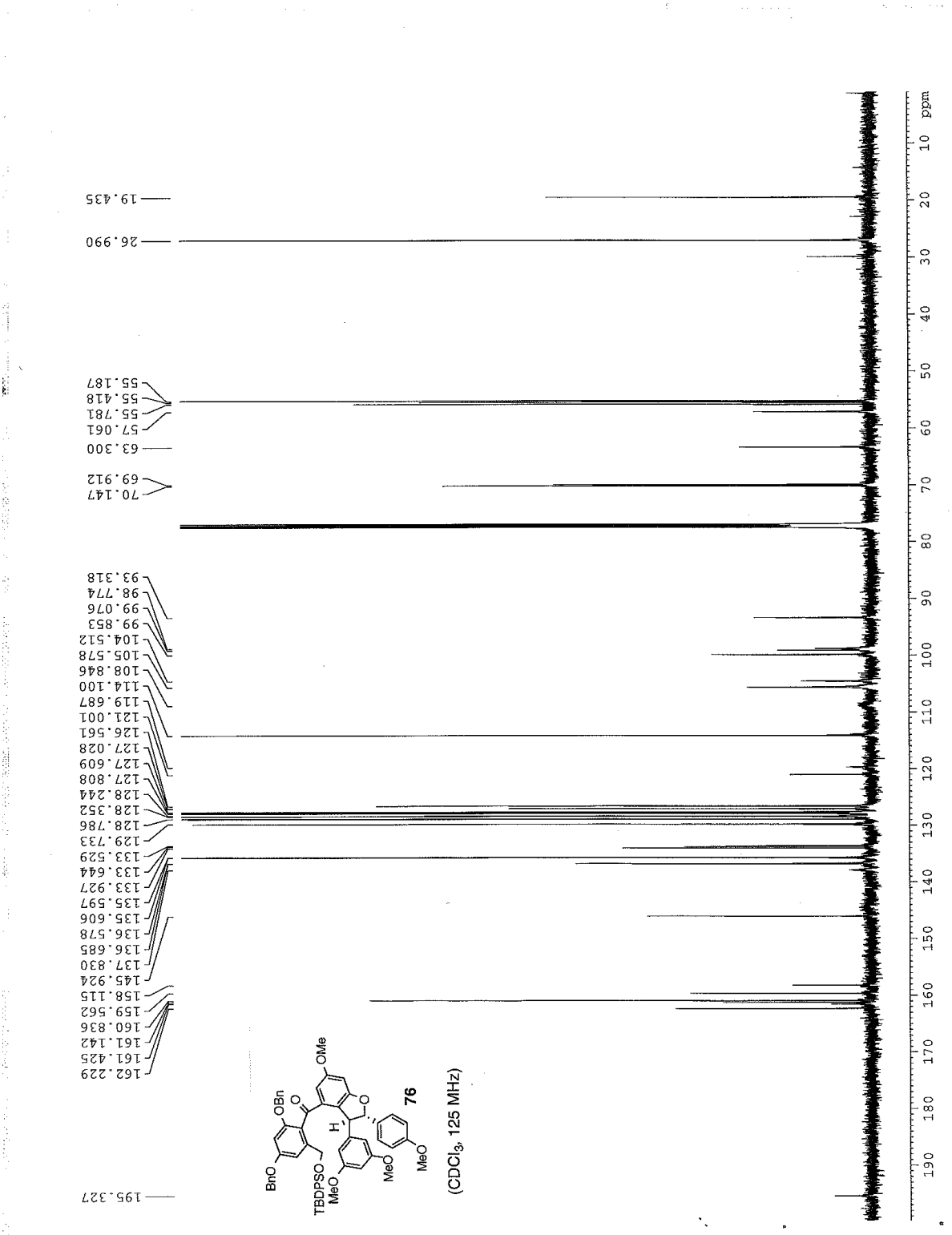

3.697
3.795
3.855
4.803
4.812
5.524
5.533
6.223
6.229
6.290
6.295
6.301
6.767
6.772
6.857
6.878
7.112
7.118
7.207
7.228
7.260
2.008
1.004
2.019
0.997
1.011
1.995
1.000
1.002
3.057
3.058
5.967
ppm
MeO
MeO
MeO
OMe
OH
O
H
73
(CDCl3, 400 MHz)

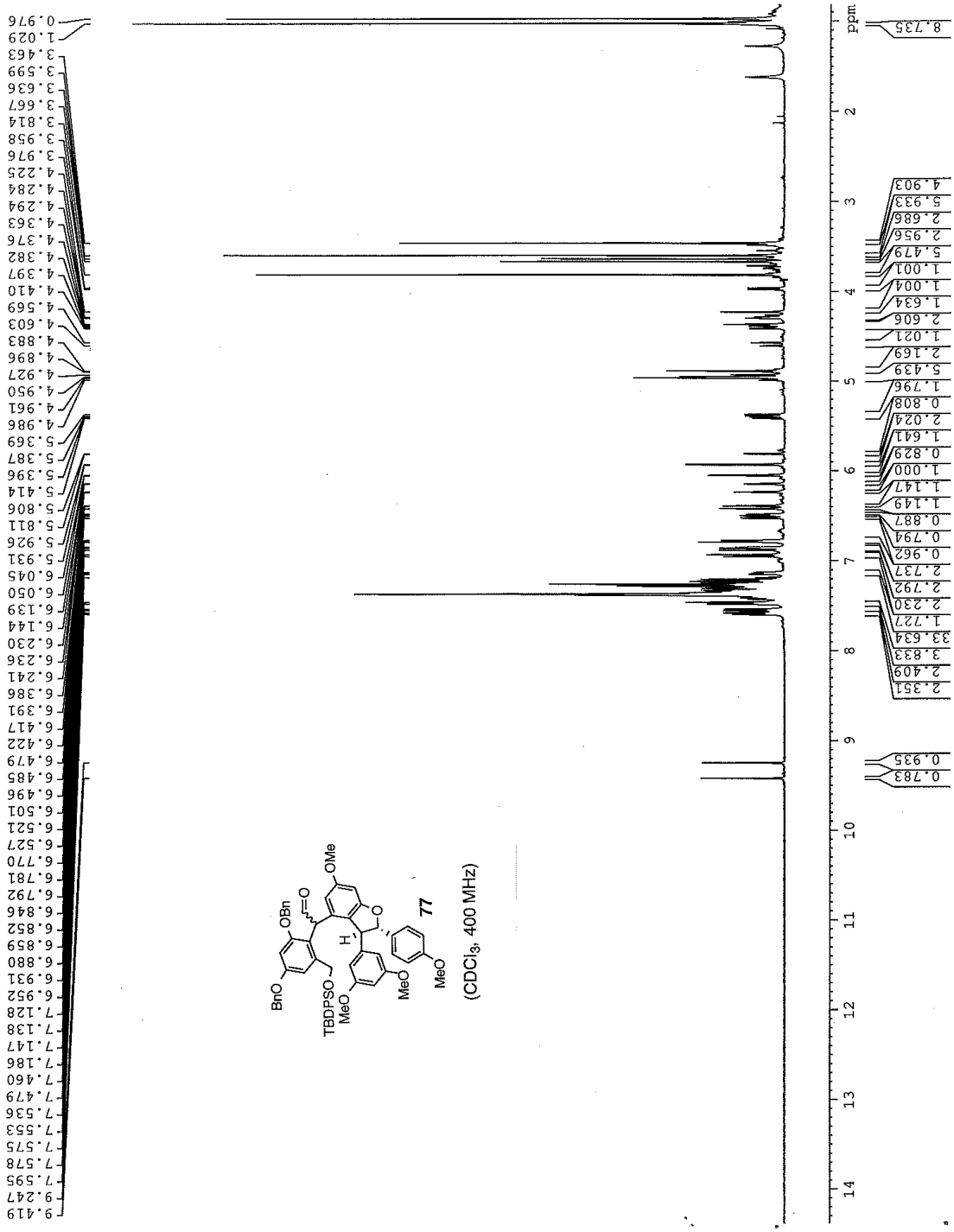

55.359
55.445
55.896
57.065
76.841
77.159
77.477
93.162
98.626
101.633
105.746
108.493
114.276
124.341
126.799
127.127
133.977
146.723
159.711
161.006
162.233
170.418
OMe
OH
O
H
MeO
MeO
MeO
73
(CDCl3, 100 MHz)
ppm

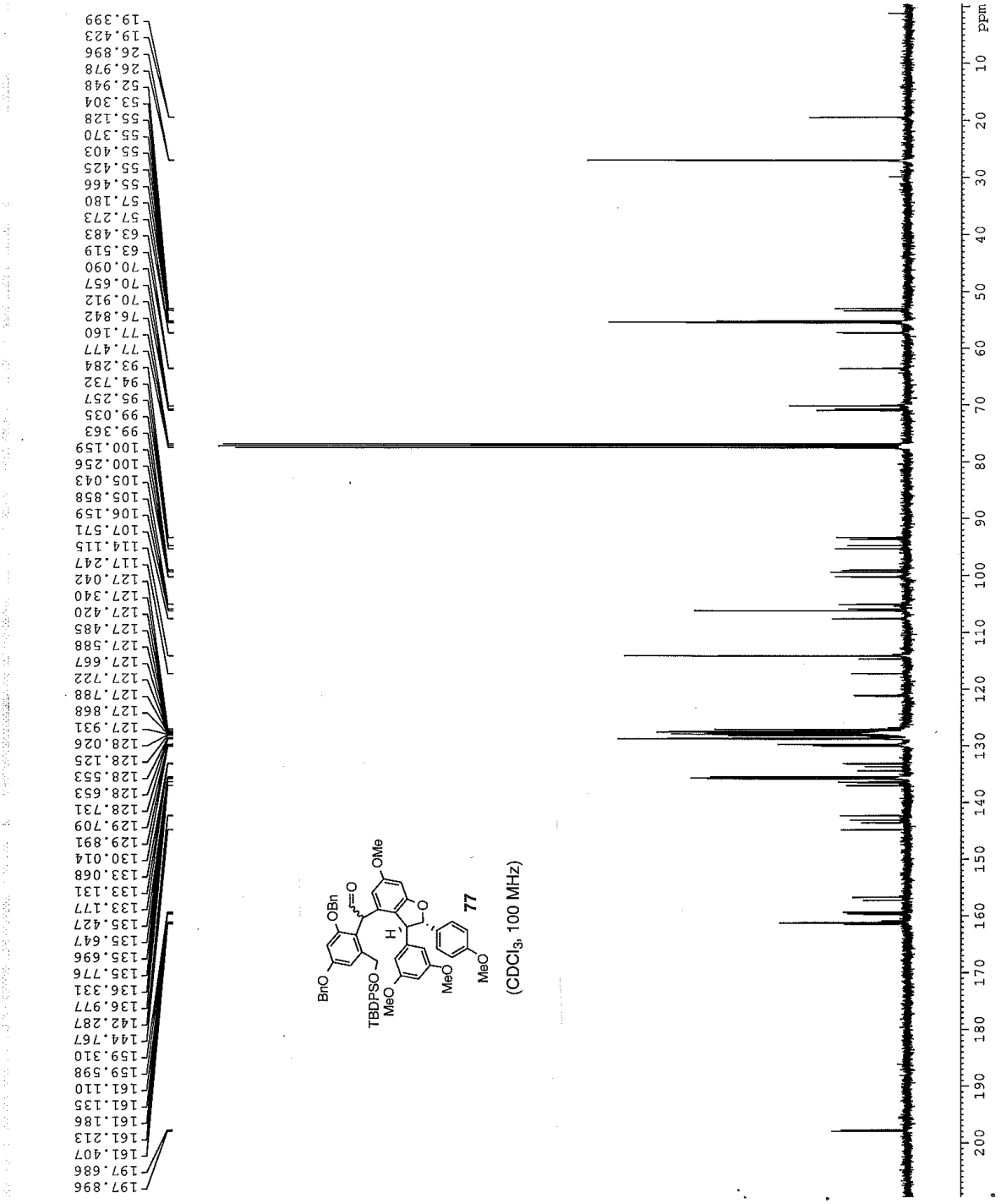

3.634
3.758
3.865
4.850
4.872
4.879
4.883
4.889
4.918
5.010
5.043
5.095
5.222
5.255
5.467
5.479
6.125
6.131
6.253
6.259
6.264
6.486
6.492
6.538
6.545
6.747
6.753
6.846
6.867
7.181
7.186
7.239
7.260
7.302
7.462
OBn
Br
OMe
O
O
H
MeO
MeO
MeO
75
(CDCl3, 400 MHz)
6.080
2.908
3.098
2.948
1.107
1.924
1.007
1.005
2.002
1.026
0.962
1.000
1.018
2.074
0.981
2.494
9.139
2.168
ppm

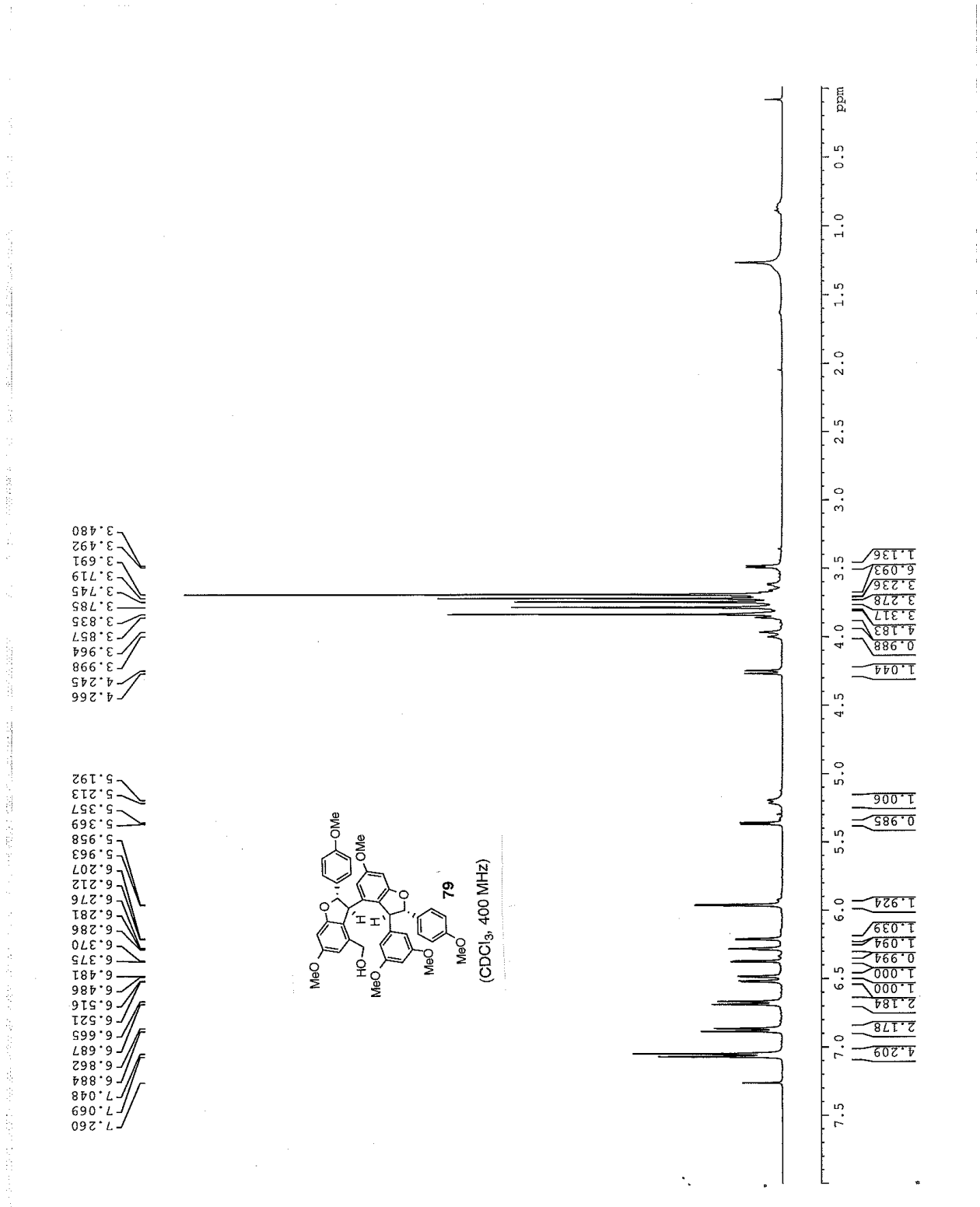

165.403
162.284
161.049
161.026
159.720
158.806
155.925
146.532
137.136
136.507
136.477
133.692
128.756
128.729
128.292
128.103
127.747
127.102
127.059
123.095
114.250
108.327
107.379
105.405
104.658
101.970
101.007
98.577
93.157
77.413
77.160
76.905
71.033
70.406
66.316
57.215
55.921
55.401
55.323
OBn
Br
OMe
BnO
MeO
MeO
MeO
75
(CDCl3, 125 MHz)
ppm

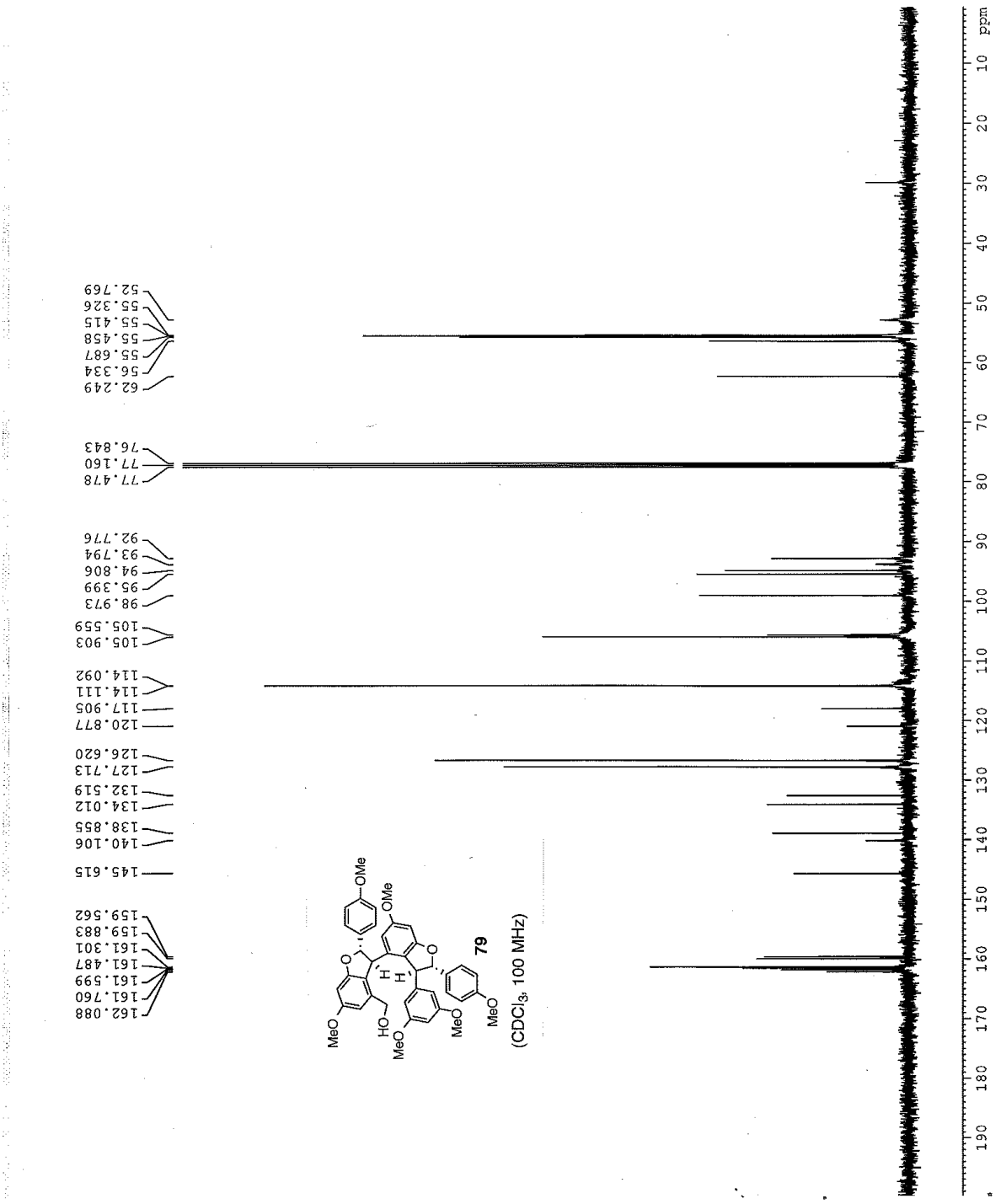

0.998
3.551
3.745
3.769
4.254
4.265
4.677
4.706
4.733
4.758
4.973
4.996
5.012
5.036
5.345
6.012
6.200
6.316
6.320
6.686
6.690
6.741
6.758
6.836
6.844
6.910
7.100
7.115
7.176
7.186
7.194
7.197
7.204
7.207
7.260
7.287
7.294
7.301
7.308
7.316
7.323
7.333
7.342
7.356
7.364
7.373
7.383
7.389
7.540
7.543
7.556
7.561
7.564
9.016
5.999
2.947
3.085
0.936
4.144
1.083
1.016
0.945
1.727
1.000
1.008
1.091
2.920
2.074
1.001
1.896
3.236
11.864
4.294
ppm
OMe
OBn
BnO
TBDPSO
MeO
MeO
MeO
76
(CDCl3, 500 MHz)

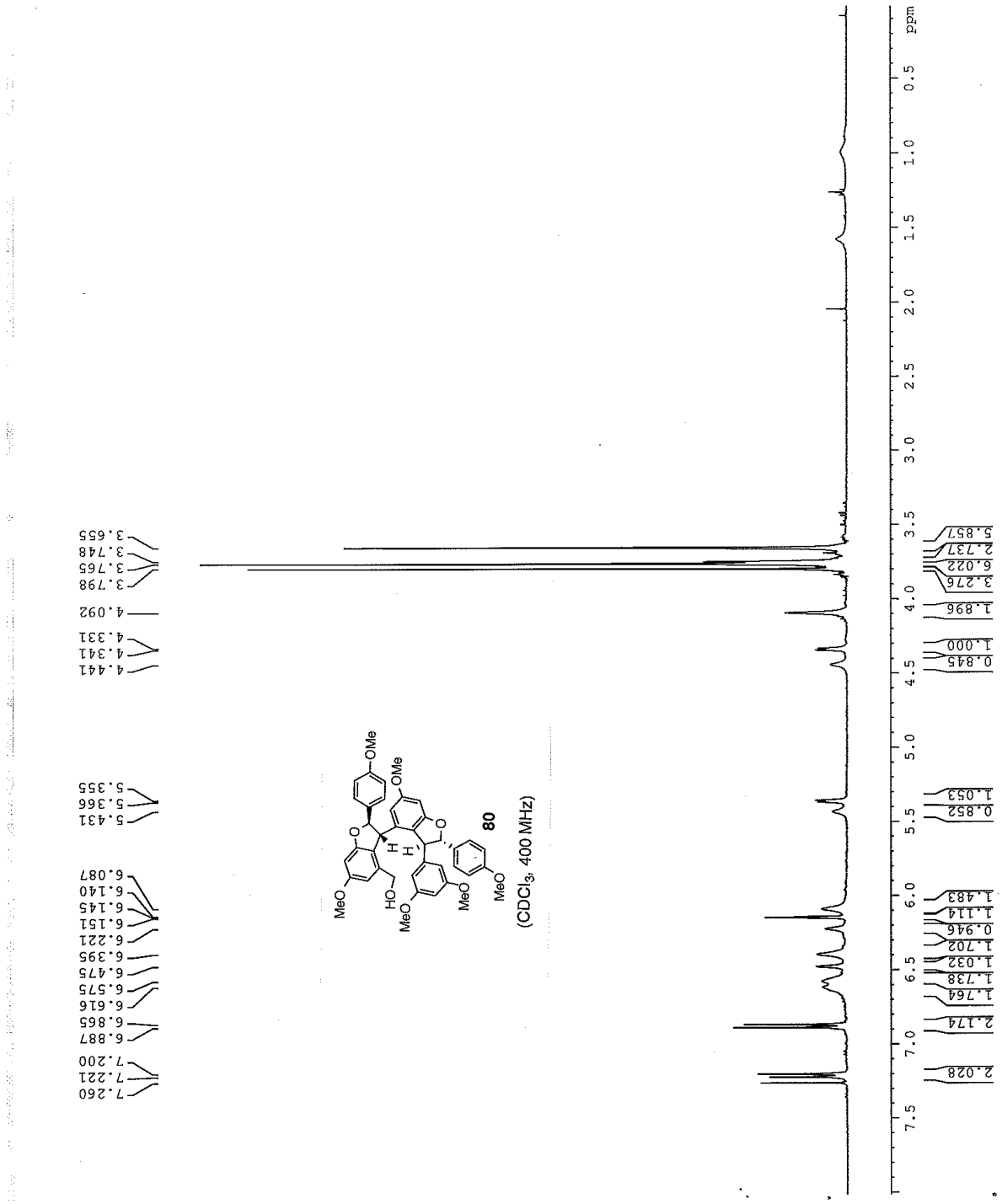

19.435
26.990
55.187
55.418
55.781
57.061
63.300
69.912
70.147
93.318
98.774
99.076
99.853
104.512
105.578
108.846
114.100
119.687
121.001
126.561
127.028
127.609
127.808
128.244
128.352
128.786
129.733
133.529
133.644
133.927
135.597
135.606
136.578
136.685
137.830
145.924
158.115
159.562
160.836
161.142
161.425
162.229
195.327
OMe
OBn
O
H
O
BnO
TBDPSO
MeO
MeO
MeO
76
(CDCl3, 125 MHz)
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

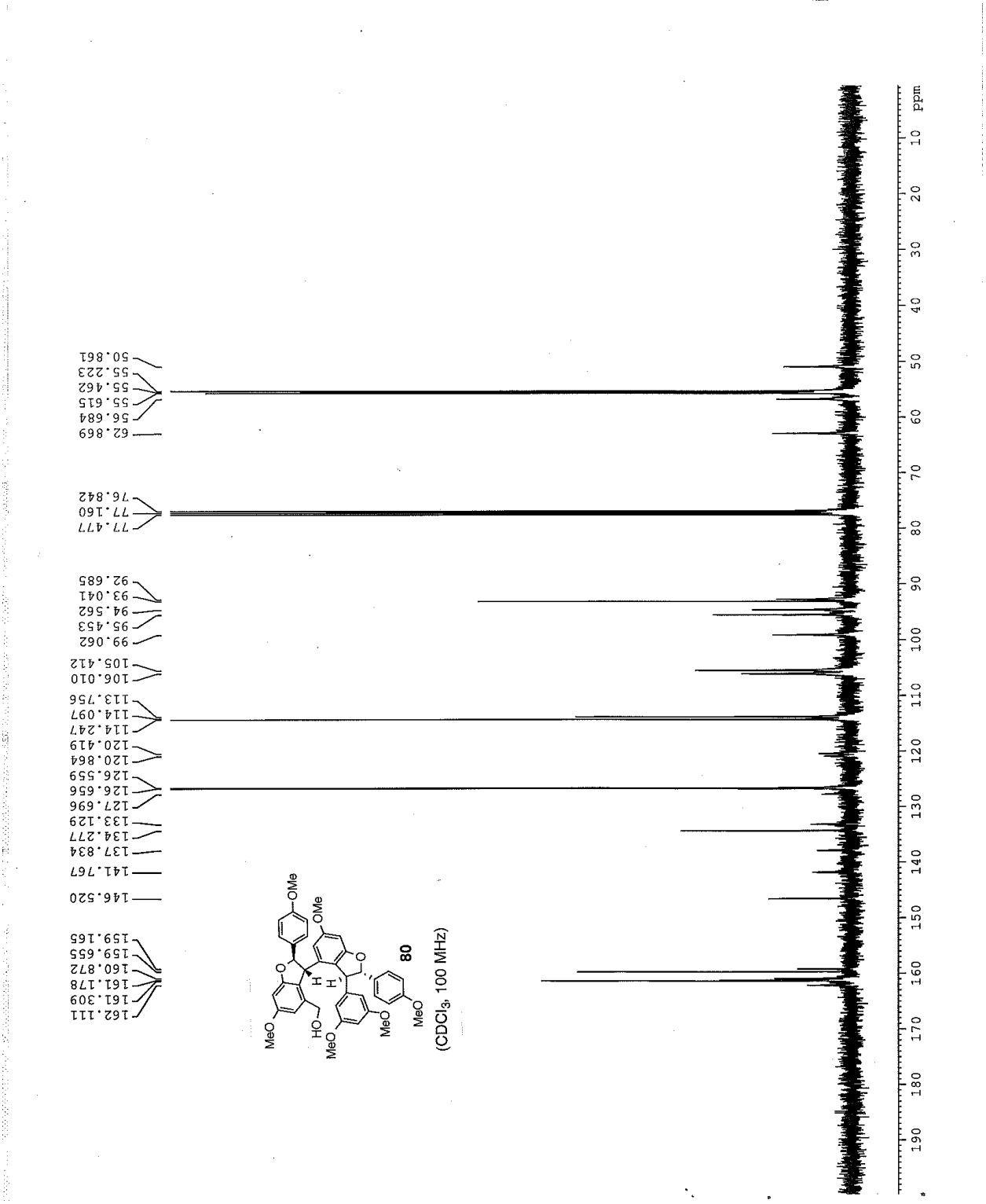

77
(CDCl3, 400 MHz)
BnO
OBn
TBDPSO
MeO
MeO
MeO
MeO
OMe
O
H
ppm

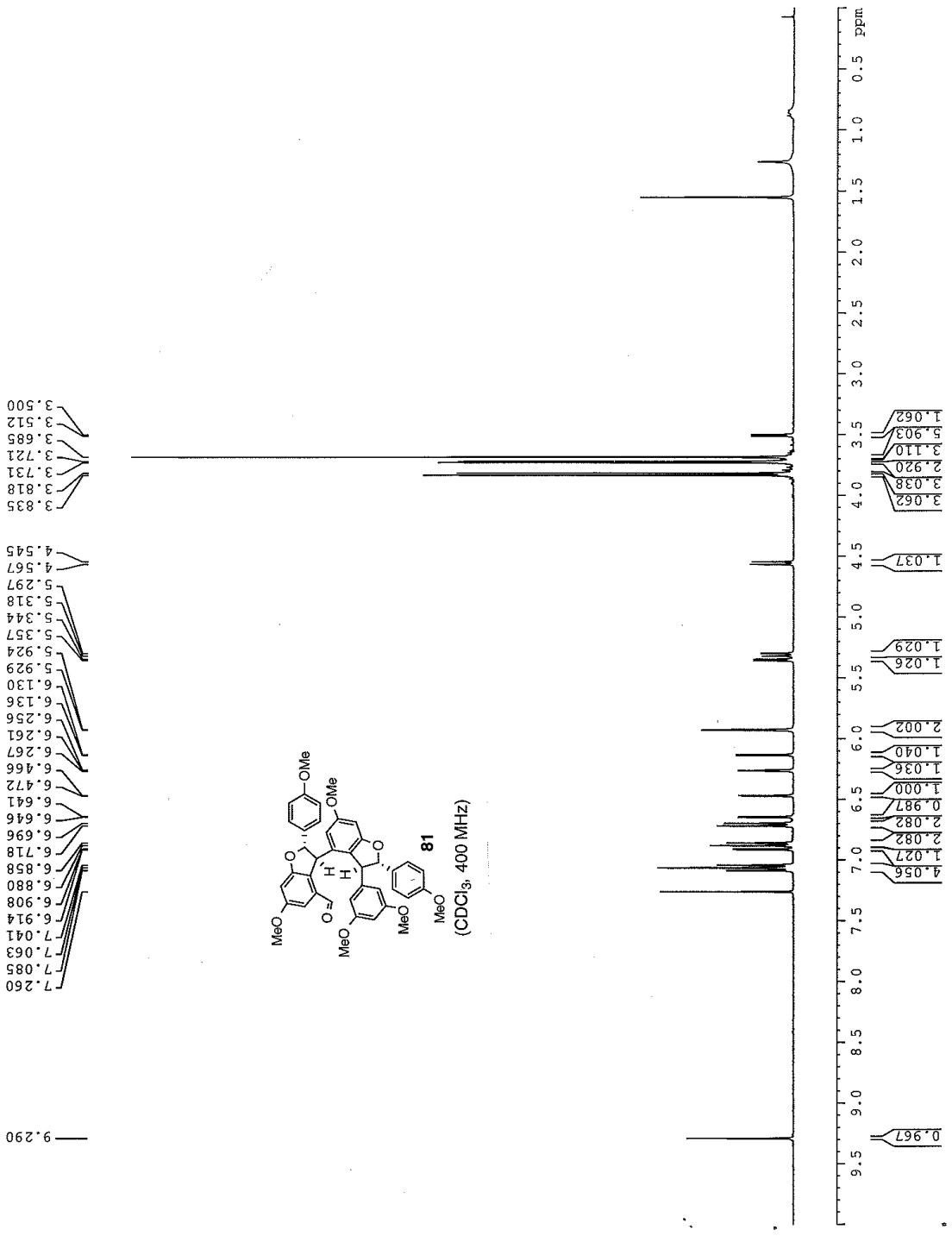

19.399
19.423
26.896
26.978
52.948
53.304
55.128
55.370
55.403
55.425
55.466
57.180
57.273
63.483
63.519
70.090
70.657
70.912
76.842
77.160
77.477
93.284
94.732
95.257
99.035
99.363
100.159
100.256
105.043
105.858
106.159
107.571
114.115
117.247
127.042
127.340
127.420
127.485
127.588
127.667
127.722
127.788
127.868
127.931
128.026
128.125
128.553
128.653
128.731
129.709
129.891
130.014
133.068
133.131
133.177
135.427
135.647
135.696
135.776
136.331
136.977
142.287
144.767
159.310
159.598
161.110
161.135
161.186
161.213
161.407
197.686
197.896
OMe
O
OBn
BnO
TBDPSO
MeO
MeO
MeO
H
77
(CDCl3, 100 MHz)
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

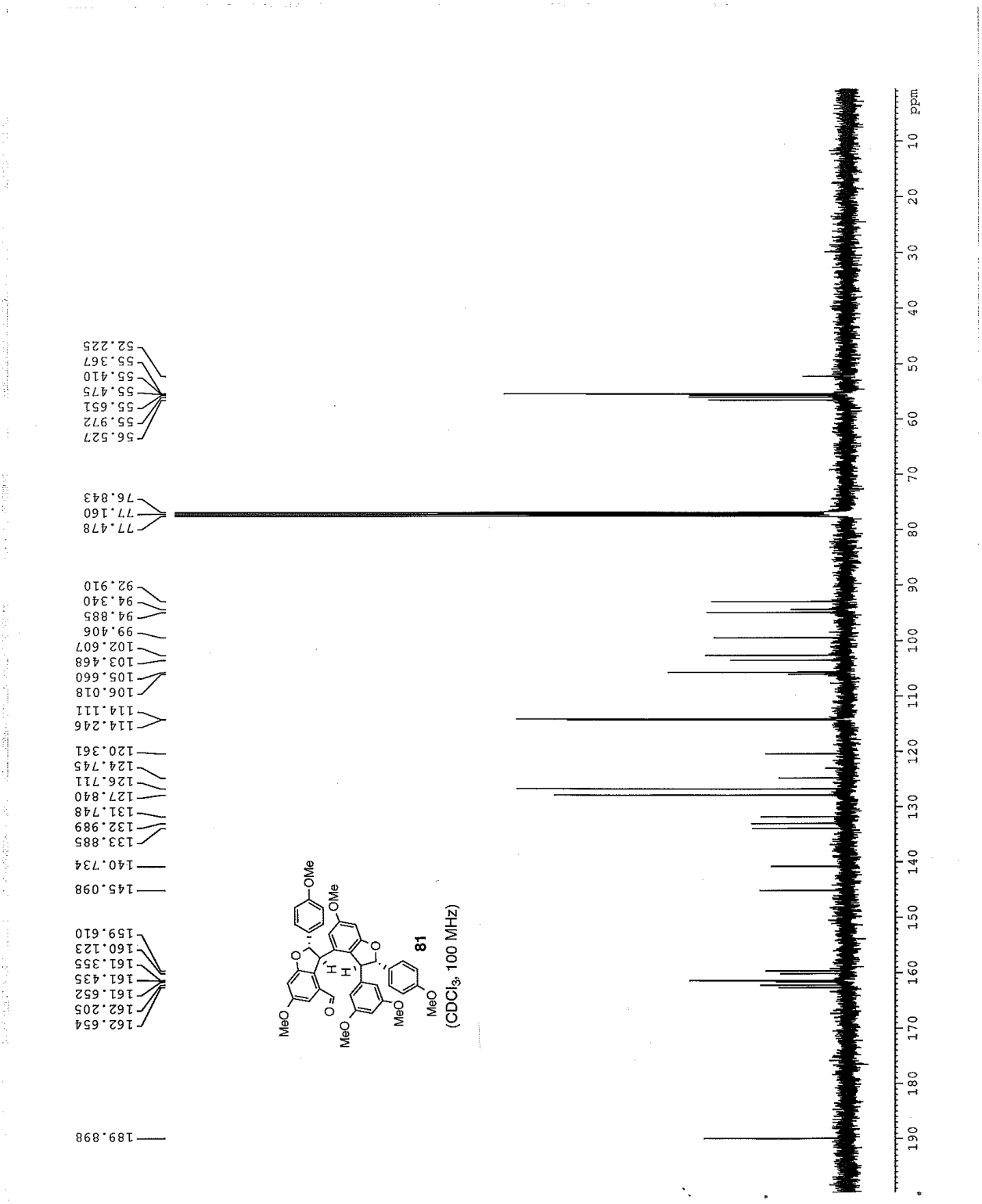

7.260
7.069
7.048
6.884
6.862
6.687
6.665
6.521
6.516
6.486
6.481
6.375
6.370
6.286
6.281
6.276
6.212
6.207
5.963
5.958
5.369
5.357
5.213
5.192
4.266
4.245
3.998
3.964
3.857
3.835
3.785
3.745
3.719
3.691
3.492
3.480
MeO
MeO
HO
MeO
MeO
MeO
OMe
OMe
H
H
O
O
79
(CDCl3, 400 MHz)
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
4.209
2.178
2.184
1.000
1.000
0.994
1.094
1.039
1.924
0.985
1.006
1.044
0.988
4.183
3.317
3.278
3.236
6.093
1.136

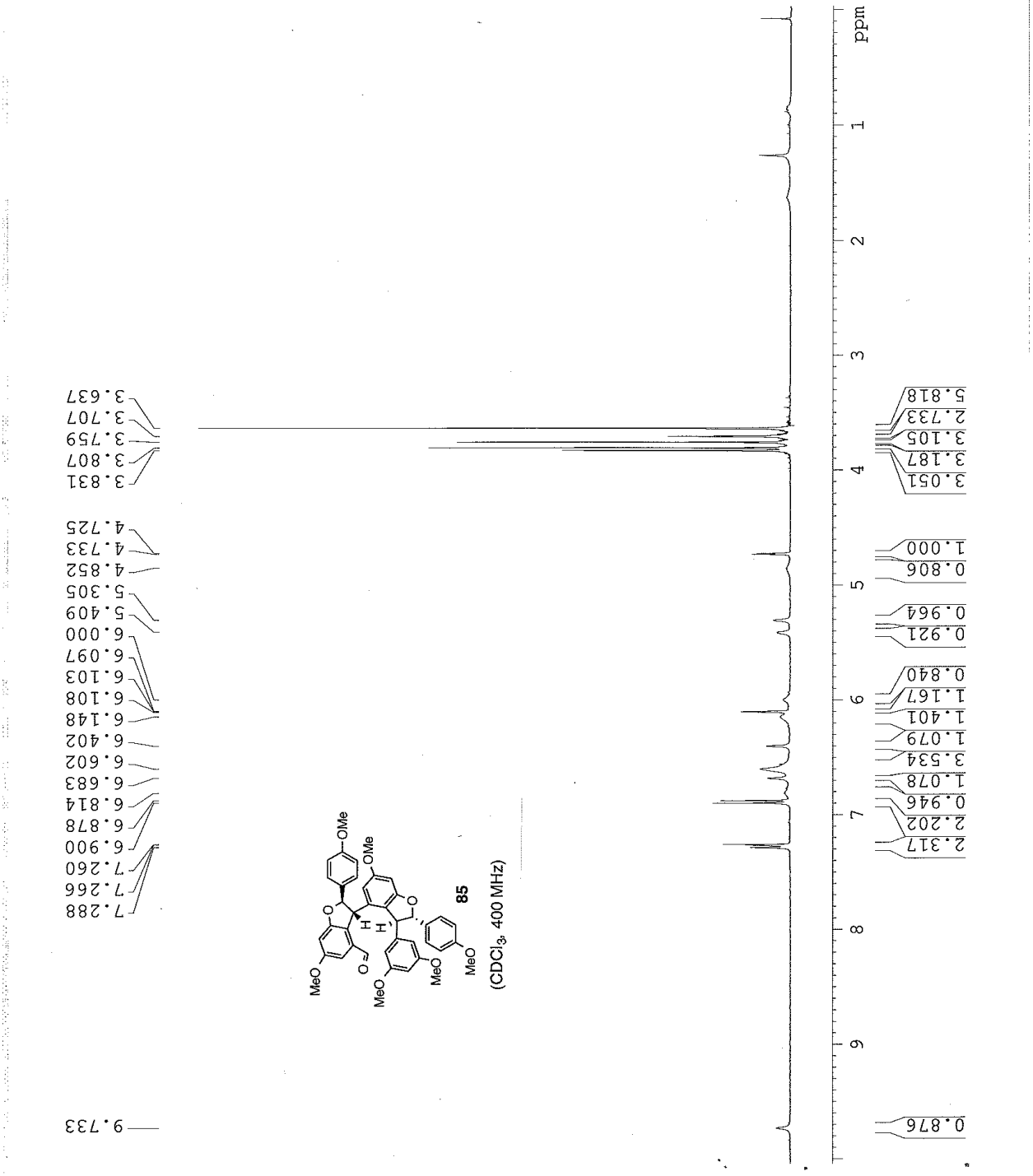

52.769
55.326
55.415
55.458
55.687
56.334
62.249
76.843
77.160
77.478
92.776
93.794
94.806
95.399
98.973
105.559
105.903
114.092
114.111
117.905
120.877
126.620
127.713
132.519
134.012
138.855
140.106
145.615
159.562
159.883
161.301
161.487
161.599
161.760
162.088
OMe
OMe
MeO
HO
MeO
MeO
MeO
H
H
79
(CDCl3, 100 MHz)
ppm

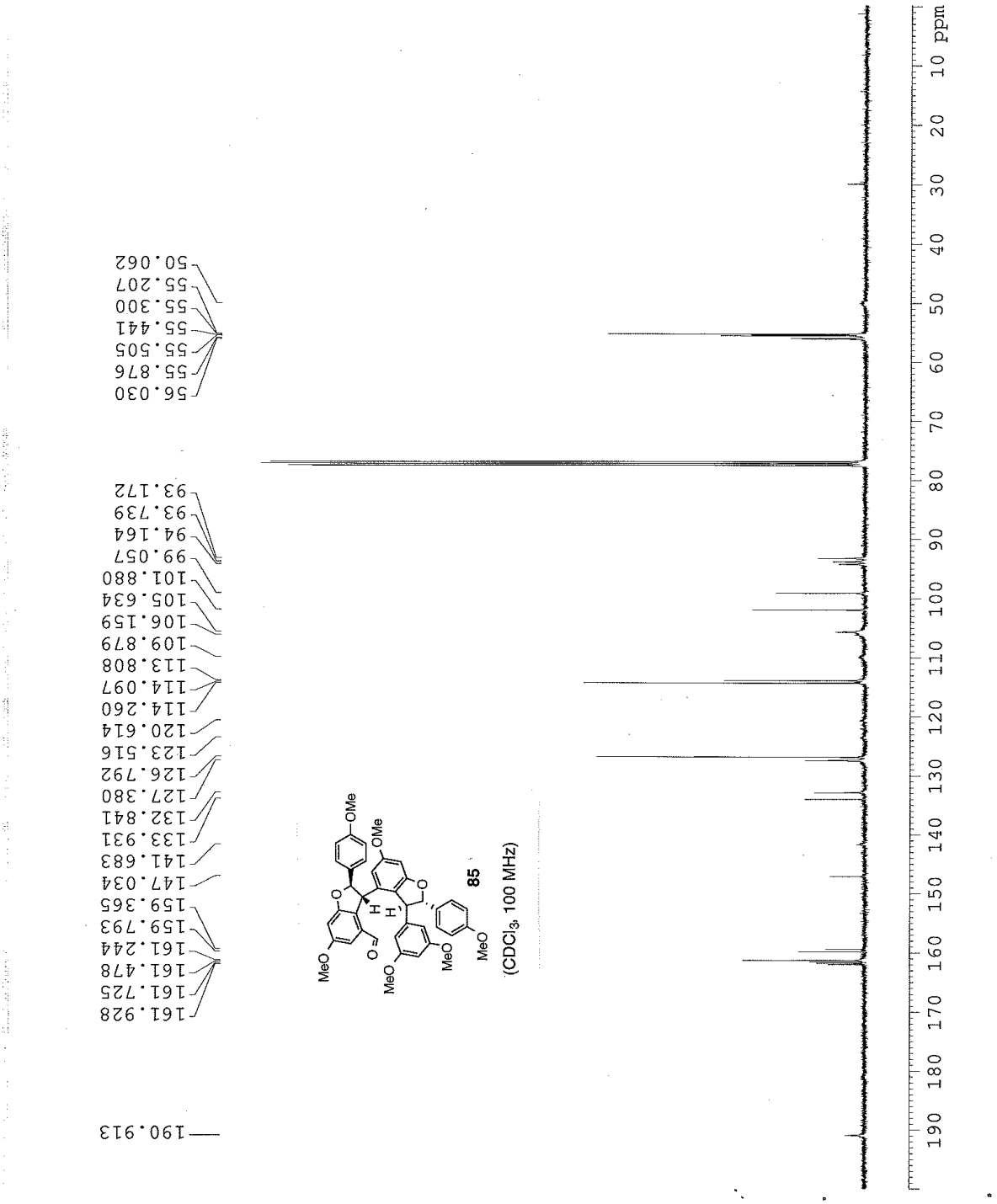

80
(CDCl3, 400 MHz)
MeO
OMe
OMe
HO
MeO
MeO
MeO
7.260
7.221
7.200
6.887
6.865
6.616
6.575
6.475
6.395
6.221
6.151
6.145
6.140
6.087
5.431
5.366
5.355
4.441
4.341
4.331
4.092
3.798
3.765
3.748
3.655
2.028
2.174
1.764
1.738
1.032
1.702
0.946
1.114
1.483
0.852
1.053
0.845
1.000
1.896
3.276
6.022
2.737
5.857
ppm

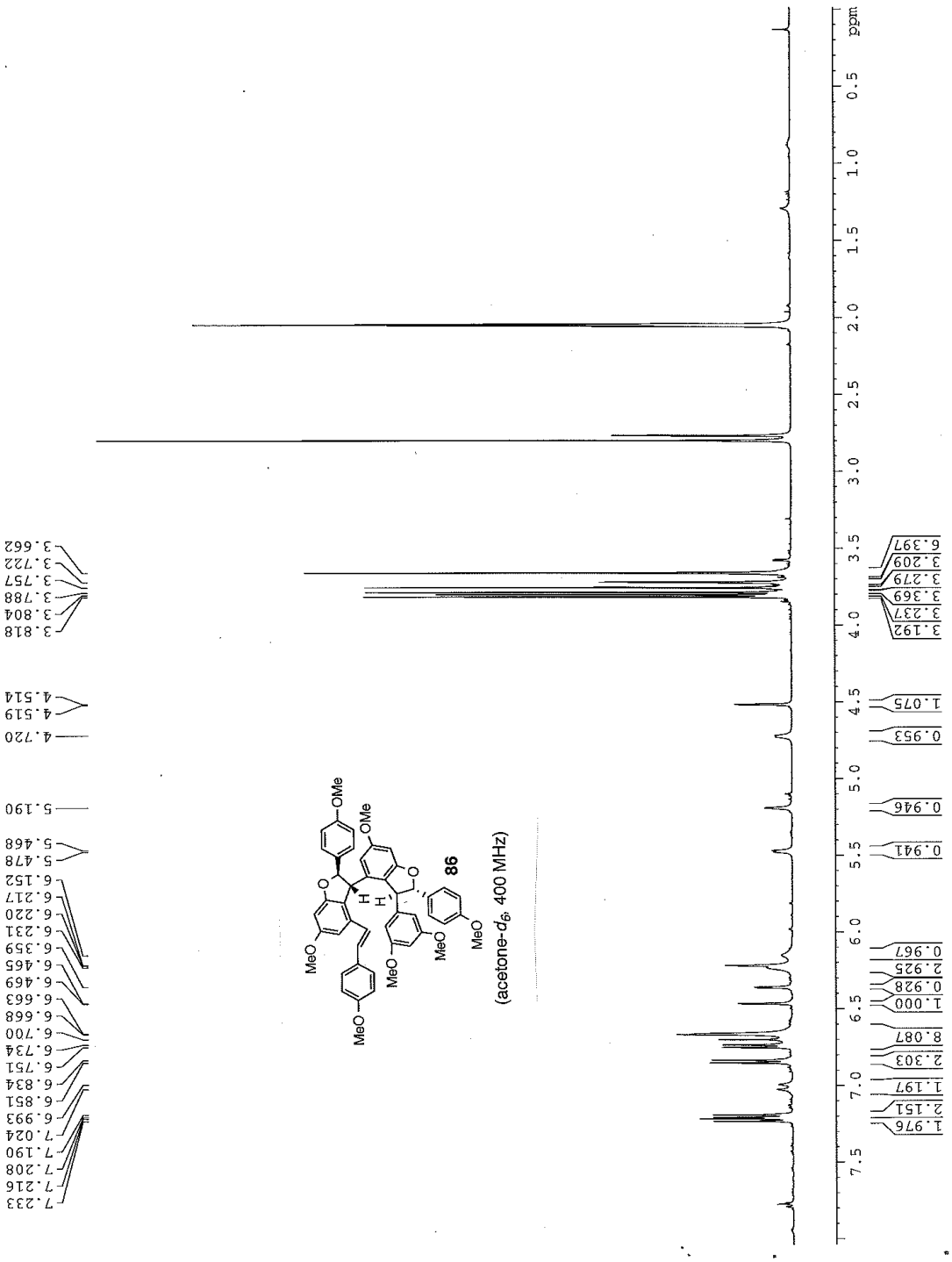

162.111
161.309
161.178
160.872
159.655
159.165
146.520
141.767
137.834
134.277
133.129
127.696
126.656
126.559
120.864
120.419
114.247
114.097
113.756
106.010
105.412
99.062
95.453
94.562
93.041
92.685
77.477
77.160
76.842
62.869
56.684
55.615
55.462
55.223
50.861
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
OMe
OMe
MeO
HO
MeO
MeO
MeO
H
H
O
O
80
(CDCl3, 100 MHz)

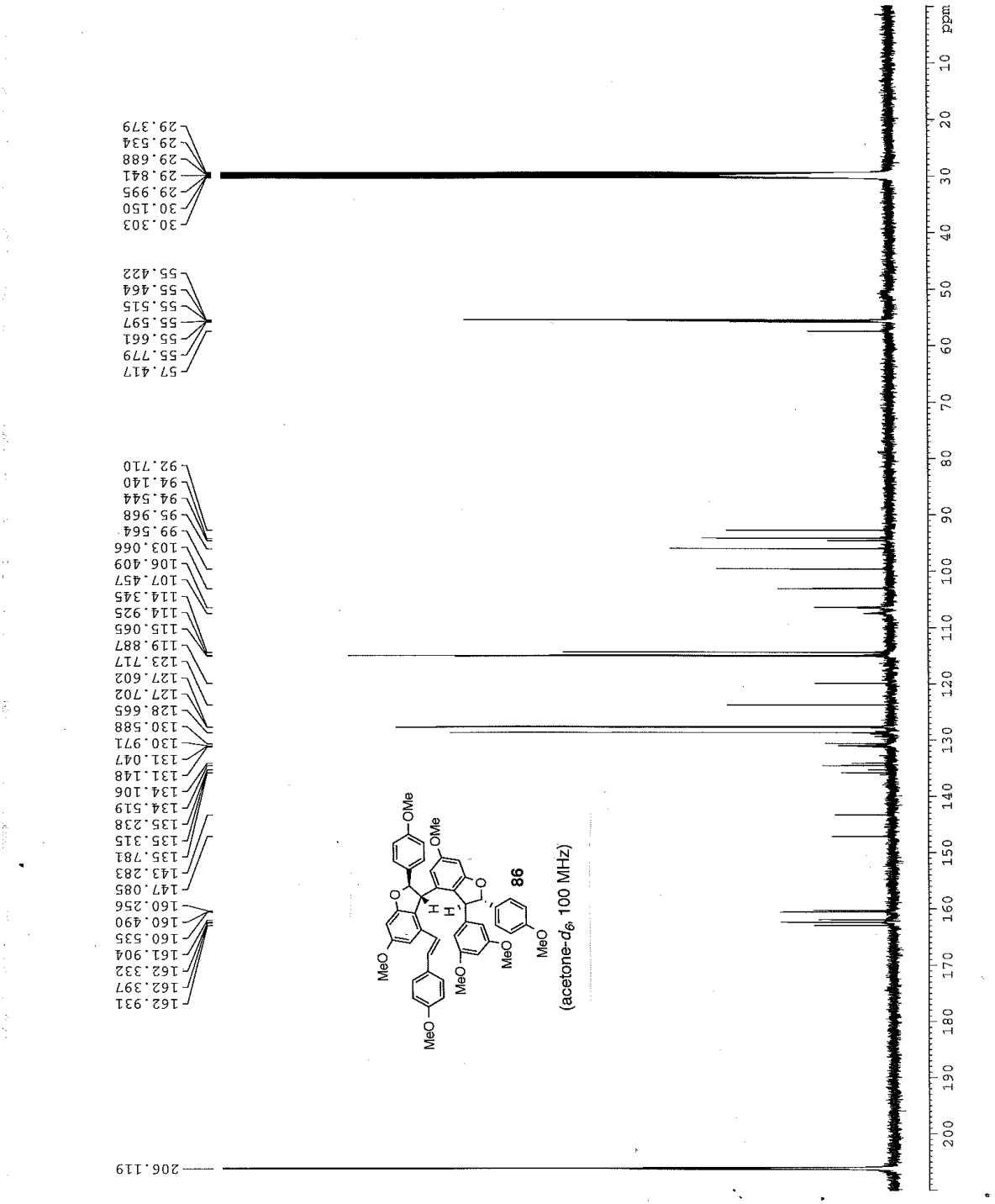

81
(CDCl3, 400 MHz)
ppm

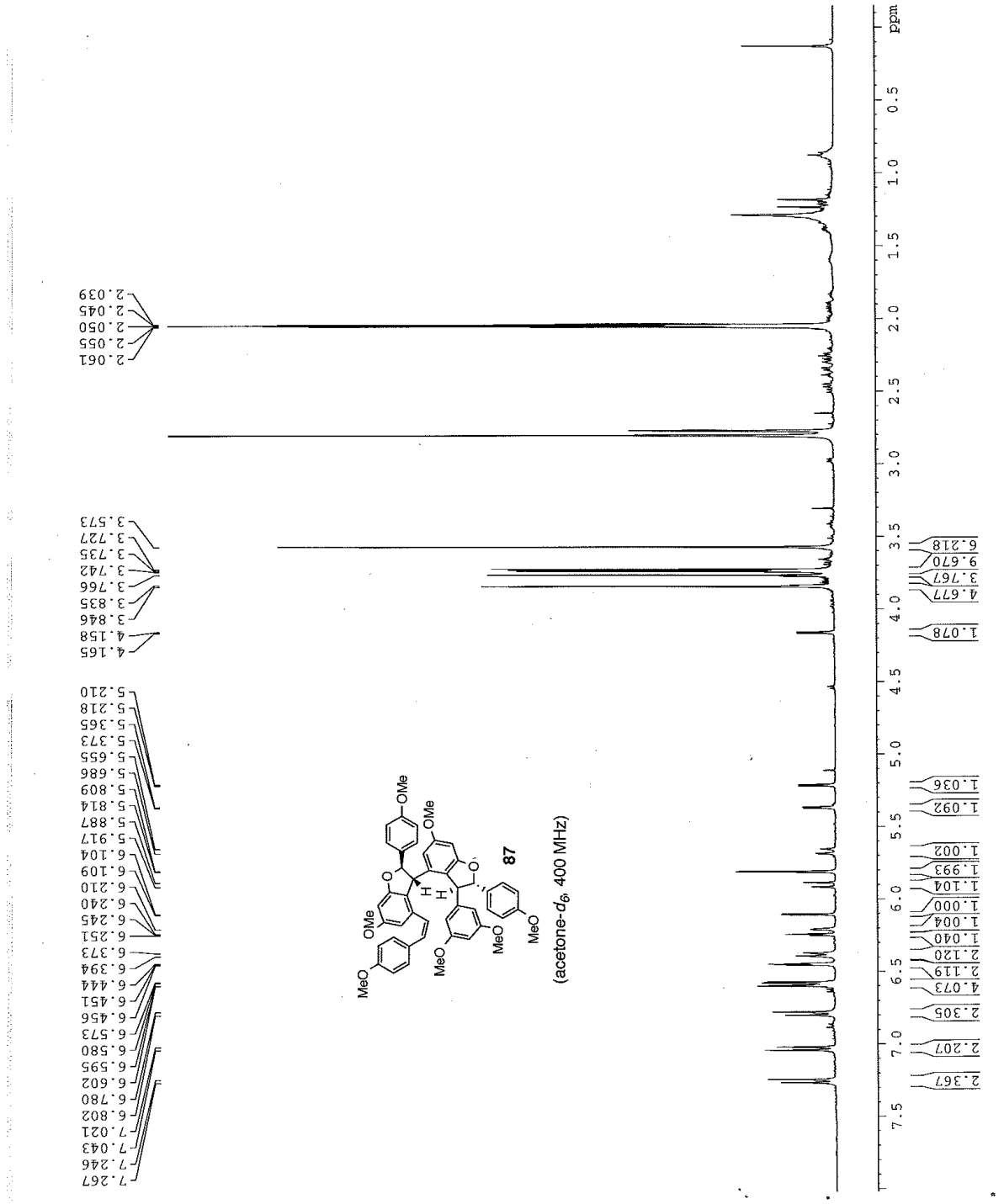

189.898
162.654
162.205
161.652
161.435
161.355
160.123
159.610
145.098
140.734
133.885
132.989
131.748
127.840
126.711
124.745
120.361
114.246
114.111
106.018
105.660
103.468
102.607
99.406
94.885
94.340
92.910
77.478
77.160
76.843
56.527
55.972
55.651
55.475
55.410
55.367
52.225
MeO
MeO
MeO
MeO
MeO
OMe
OMe
81
(CDCl3, 100 MHz)
ppm

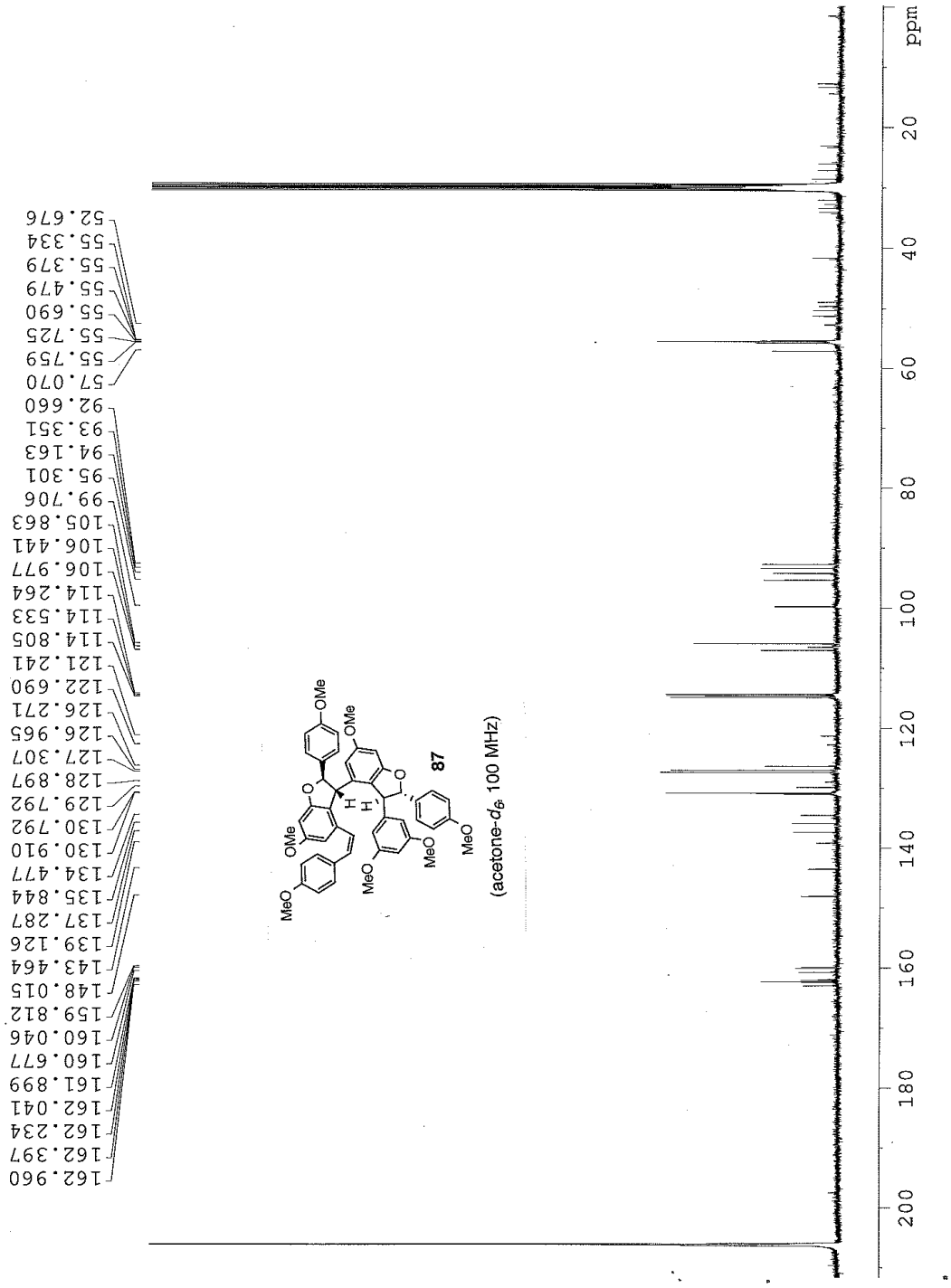

9.733
7.288
7.266
7.260
6.900
6.878
6.814
6.683
6.602
6.402
6.148
6.108
6.103
6.097
6.000
5.409
5.305
4.852
4.733
4.725
3.831
3.807
3.759
3.707
3.637
0.876
2.317
2.202
0.946
1.078
3.534
1.079
1.401
1.167
0.840
0.921
0.964
0.806
1.000
3.051
3.187
3.105
2.733
5.818
ppm
1
2
3
4
5
6
7
8
9
MeO
OMe
OMe
MeO
MeO
MeO
O
O
H
H
O
85
(CDCl3, 400 MHz)

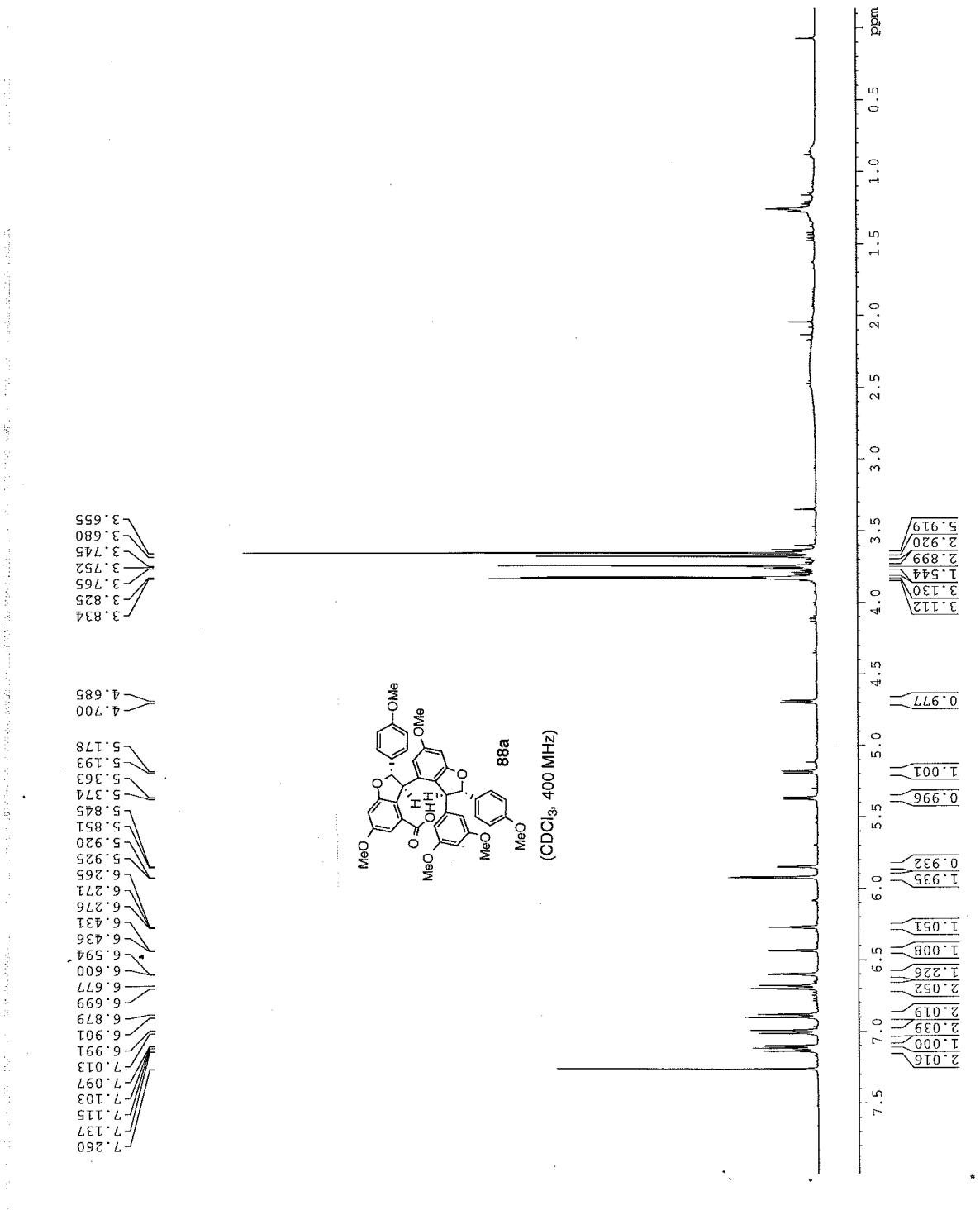

190.913
161.928
161.725
161.478
161.244
159.793
159.365
147.034
141.683
133.931
132.841
127.380
126.792
123.516
120.614
114.260
114.097
113.808
109.879
106.159
105.634
101.880
99.057
94.164
93.739
93.172
56.030
55.876
55.505
55.441
55.300
55.207
50.062
OMe
OMe
MeO
MeO
MeO
MeO
H
H
O
O
O
85
(CDCl3, 100 MHz)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

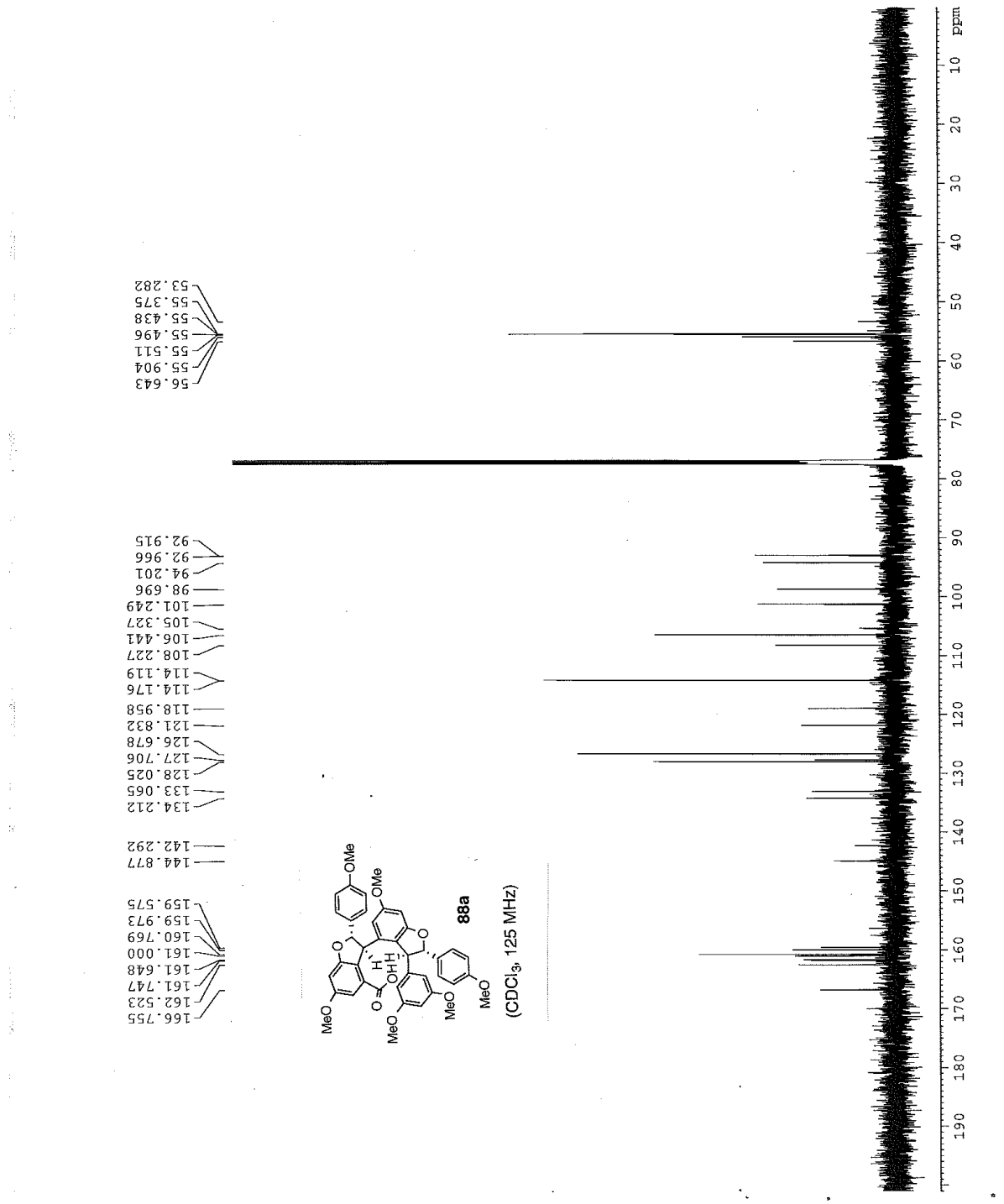

86
(acetone-d_6, 400 MHz)
MeO
OMe
H
O
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.976
2.151
1.197
2.303
8.087
1.000
0.928
2.925
0.967
0.946
0.941
0.953
1.075
3.192
3.237
3.369
3.279
3.209
6.397
3.662
3.722
3.757
3.788
3.804
3.818
4.514
4.519
4.720
5.190
5.468
5.478
6.152
6.217
6.220
6.231
6.359
6.465
6.469
6.663
6.668
6.700
6.734
6.751
6.834
6.851
6.993
7.024
7.190
7.208
7.216
7.233

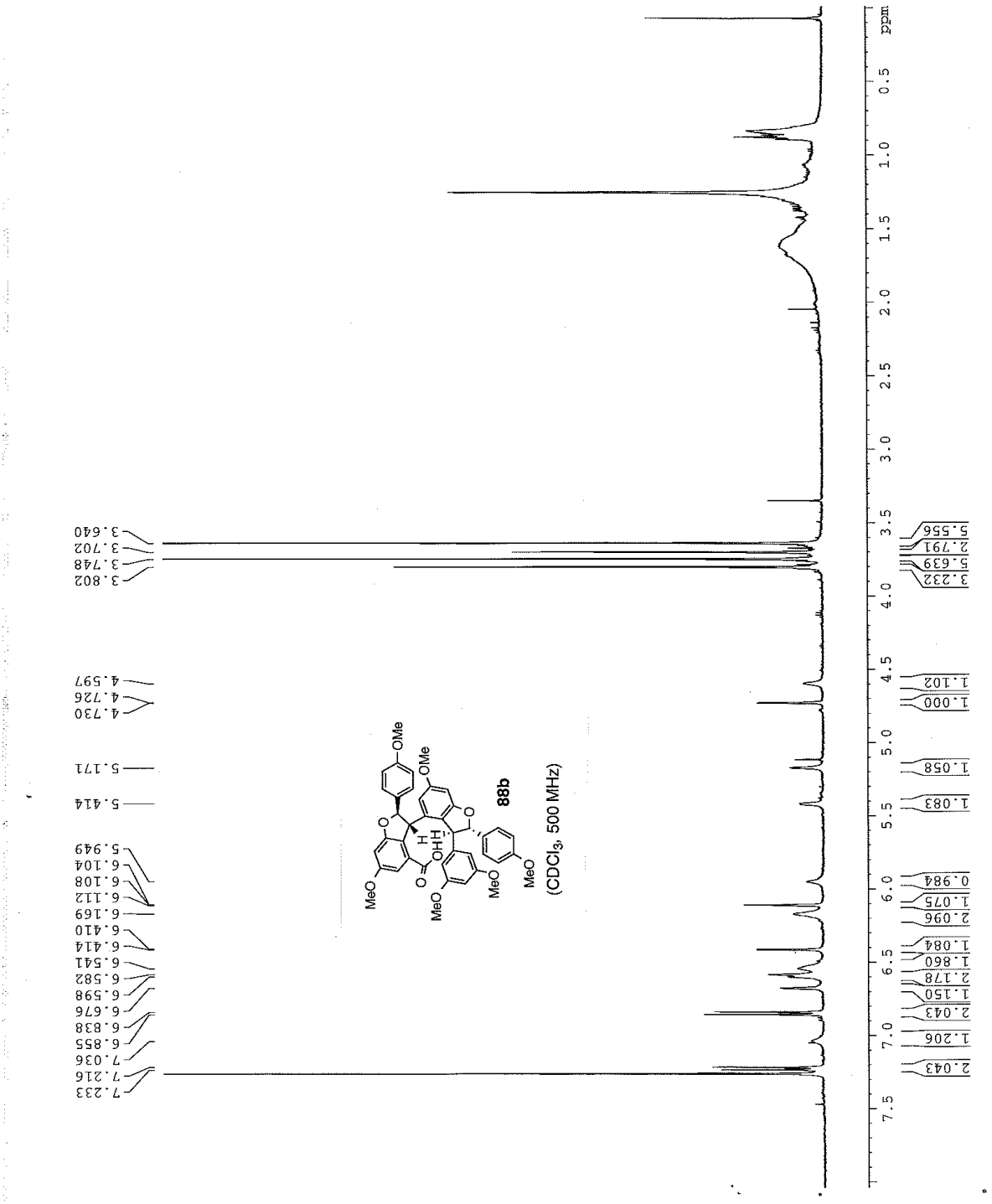

206.119
162.931
162.397
162.332
161.904
160.535
160.490
160.256
147.085
143.283
135.781
135.315
135.238
134.519
134.106
131.148
131.047
130.971
130.588
128.665
127.702
127.602
123.717
119.887
115.065
114.925
114.345
107.457
106.409
103.066
99.564
95.968
94.544
94.140
92.710
57.417
55.779
55.661
55.597
55.515
55.464
55.422
30.303
30.150
29.995
29.841
29.688
29.534
29.379
MeO
MeO
MeO
MeO
MeO
MeO
H
H
O
O
86
(acetone-d_6, 100 MHz)
ppm

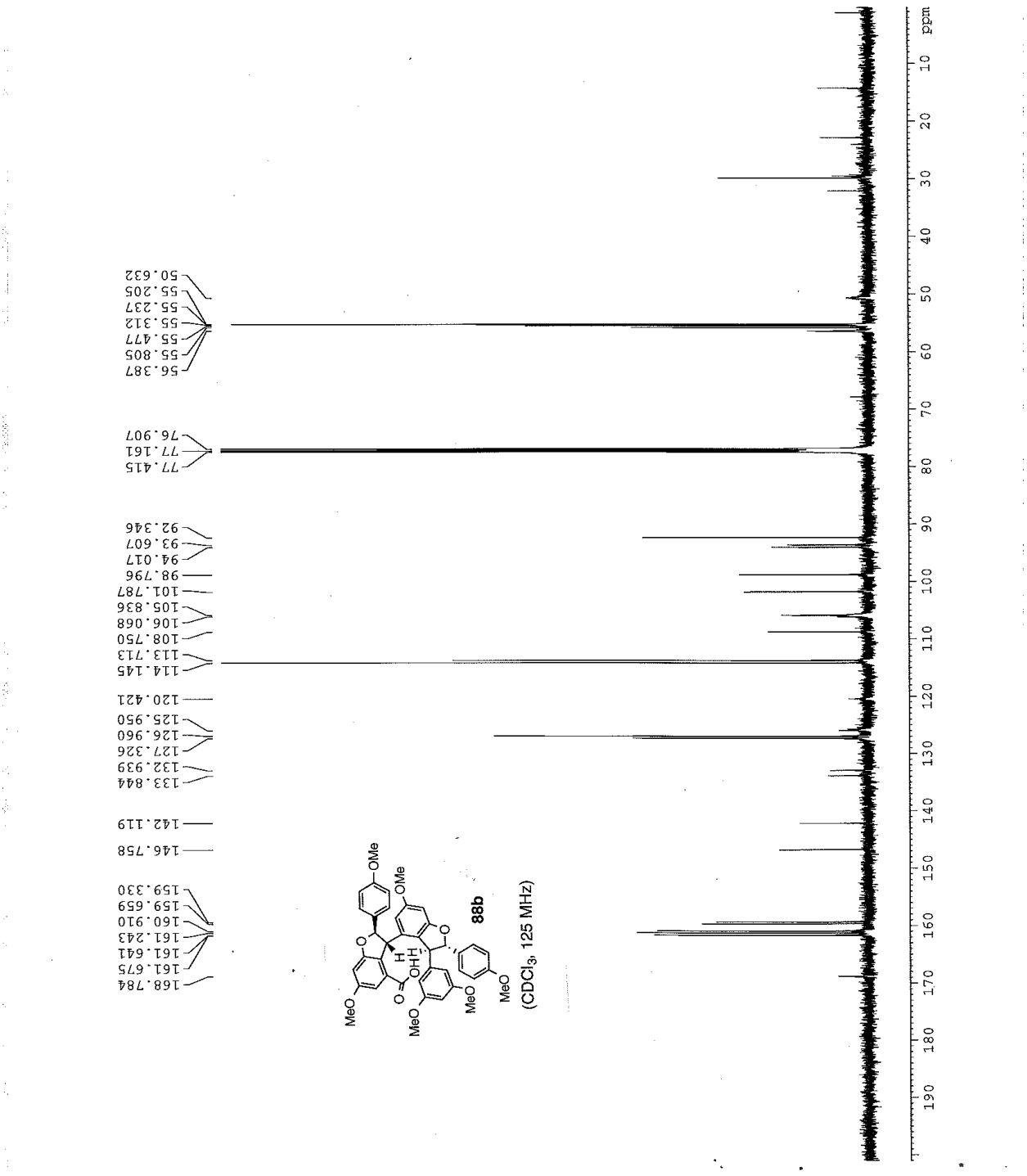

87
(acetone-d_6, 400 MHz)
ppm

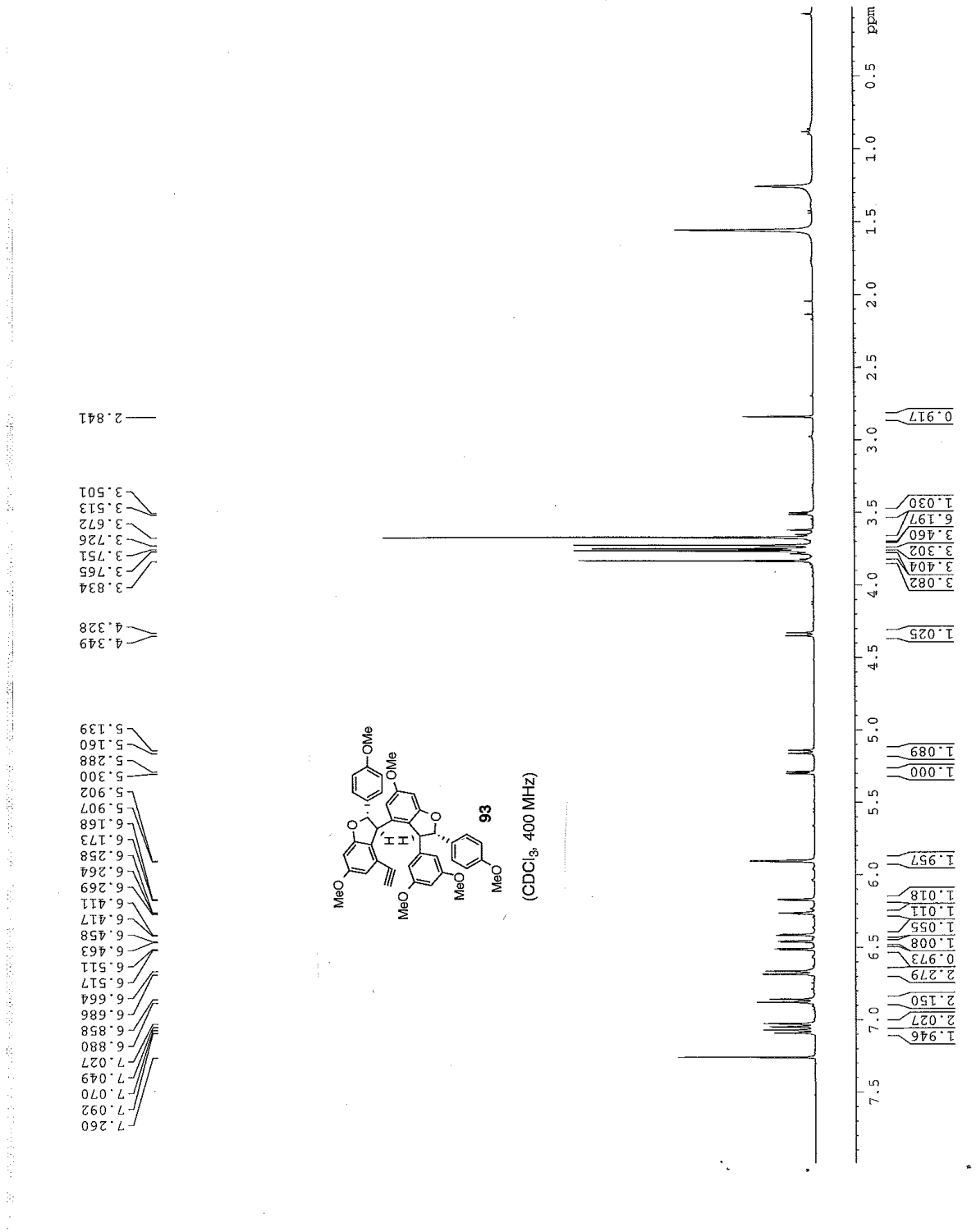

ppm
200
180
160
140
120
100
80
60
40
20
OMe
OMe
OMe
MeO
MeO
MeO
MeO
H
H
O
O
87
(acetone-d_6, 100 MHz)
162.960
162.397
162.234
162.041
161.899
160.677
160.046
159.812
148.015
143.464
139.126
137.287
135.844
134.477
130.910
130.792
129.792
128.897
127.307
126.965
126.271
122.690
121.241
114.805
114.533
114.264
106.977
106.441
105.863
99.706
95.301
94.163
93.351
92.660
57.070
55.759
55.725
55.690
55.479
55.379
55.334
52.676

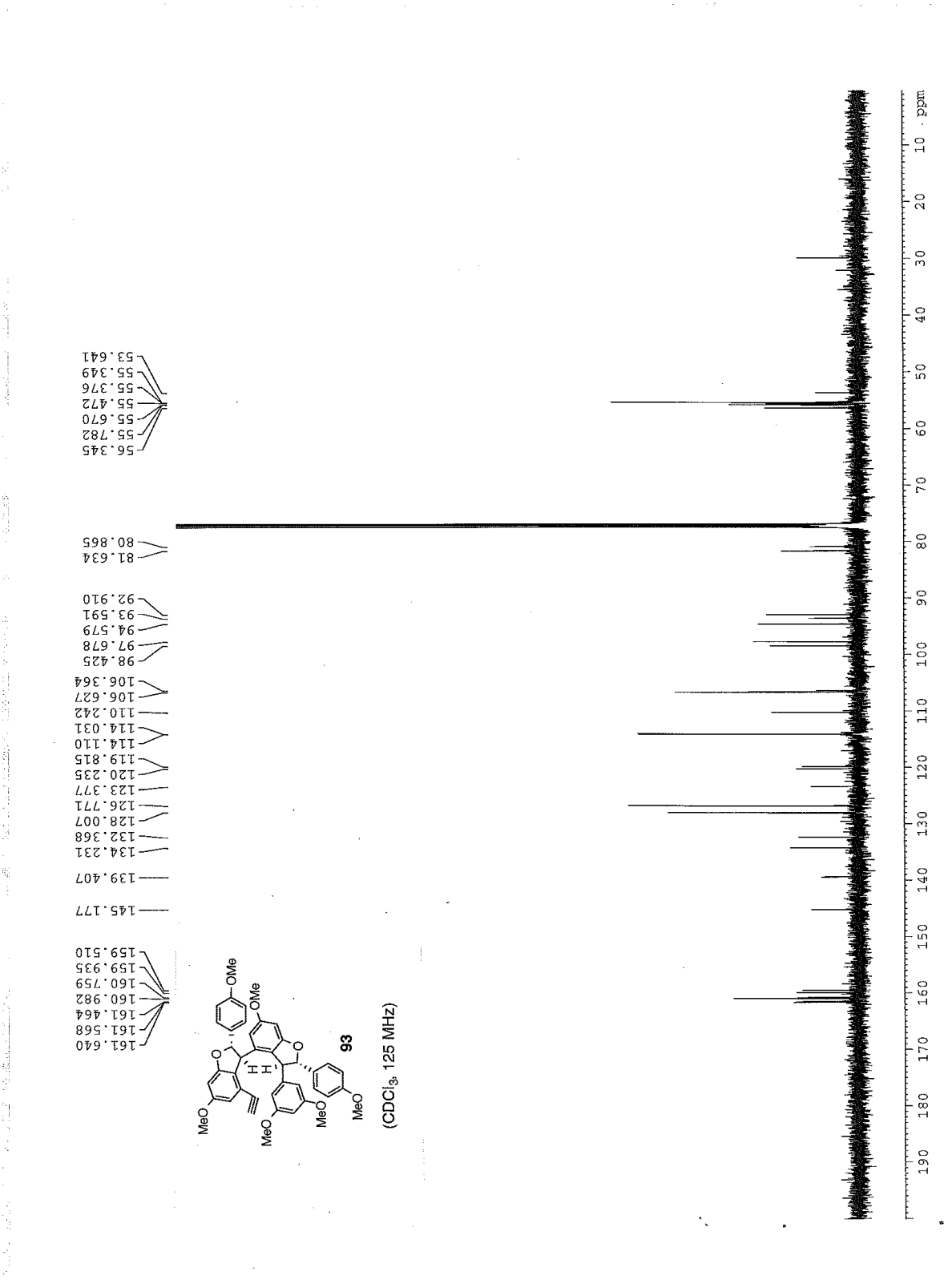

88a
(CDCl3, 400 MHz)
MeO
OMe
OH
H
O
ppm
7.260
7.137
7.115
7.103
7.097
7.013
6.991
6.901
6.879
6.699
6.677
6.600
6.594
6.436
6.431
6.276
6.271
6.265
5.925
5.920
5.851
5.845
5.374
5.363
5.193
5.178
4.700
4.685
3.834
3.825
3.765
3.752
3.745
3.680
3.655
3.112
3.130
1.544
2.899
2.920
5.919
0.977
1.001
0.996
1.935
0.932
1.051
1.008
1.226
2.052
2.019
2.039
1.000
2.016

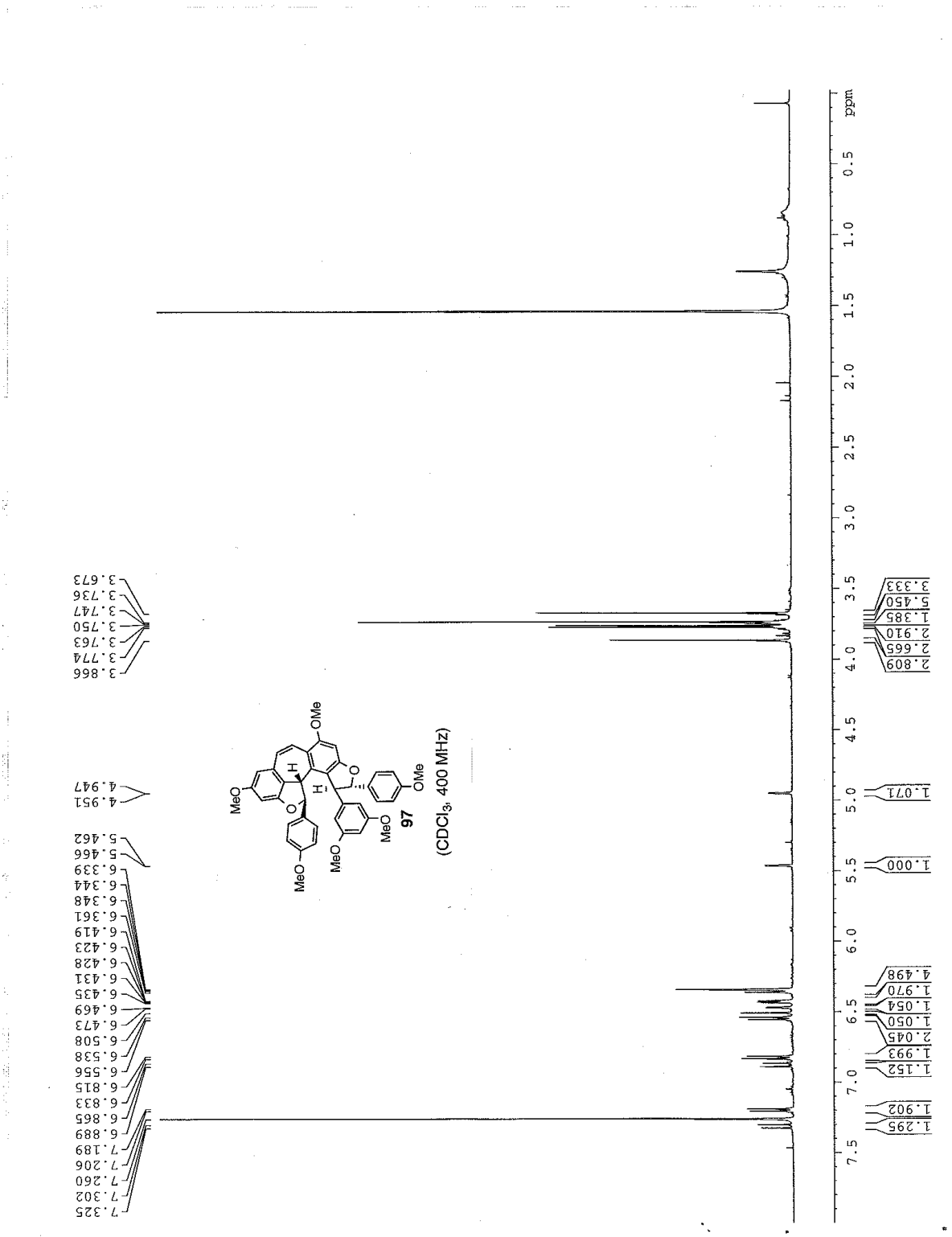

166.755
162.523
161.747
161.648
161.000
160.769
159.973
159.575
144.877
142.292
134.212
133.065
128.025
127.706
126.678
121.832
118.958
114.176
114.119
108.227
106.441
105.327
101.249
98.696
94.201
92.966
92.915
56.643
55.904
55.511
55.496
55.438
55.375
53.282
OMe
OMe
MeO
MeO
MeO
MeO
OH
H
O
88a
(CDCl3, 125 MHz)
ppm

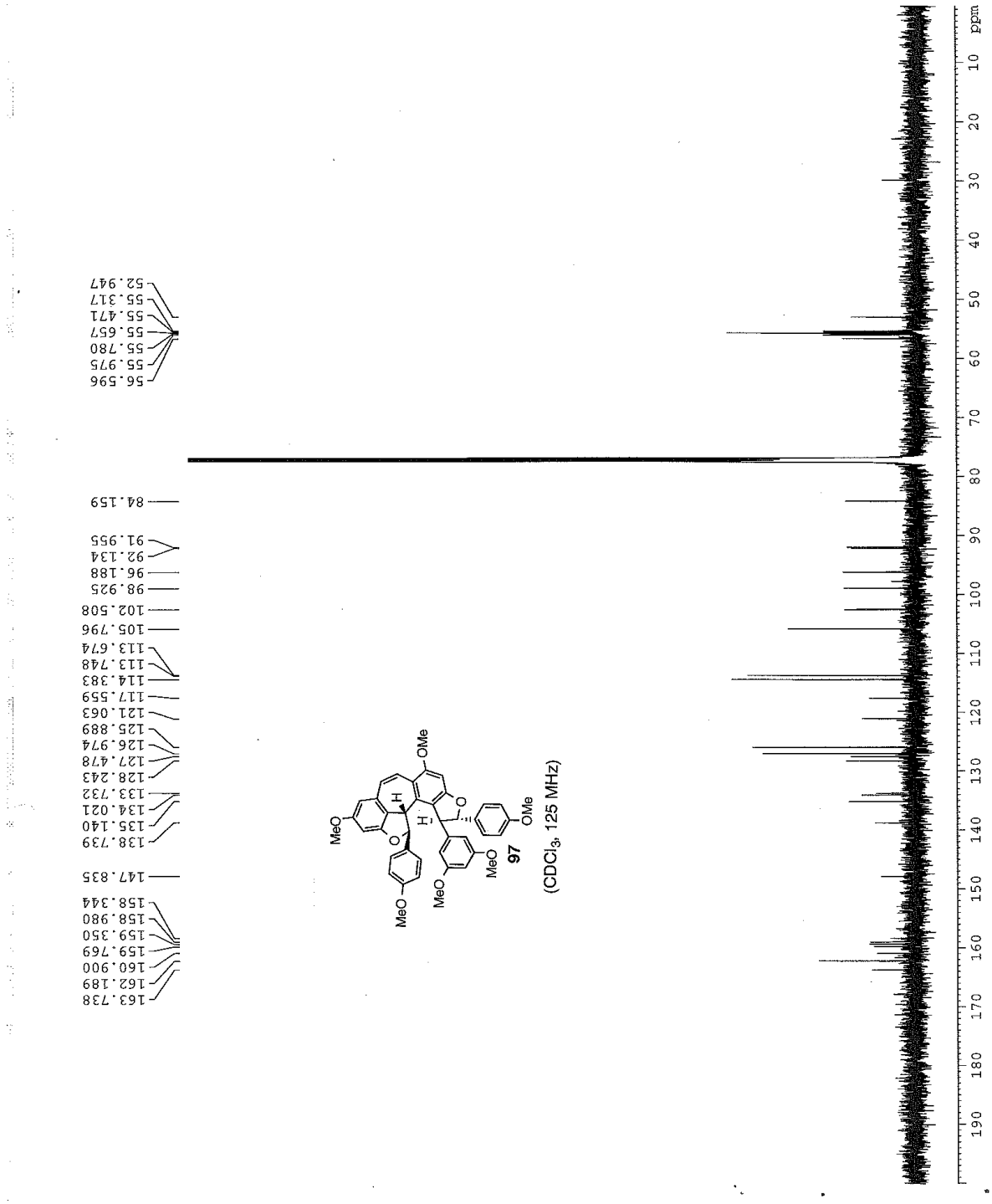

88b
(CDCl3, 500 MHz)
MeO
OMe
OH
H
O
7.233
7.216
7.036
6.855
6.838
6.676
6.598
6.582
6.541
6.414
6.410
6.169
6.112
6.108
6.104
5.949
5.414
5.171
4.730
4.726
4.597
3.802
3.748
3.702
3.640
2.043
1.206
2.043
1.150
2.178
1.860
1.084
2.096
1.075
0.984
1.058
1.083
1.102
1.000
3.232
5.639
2.791
5.556
ppm

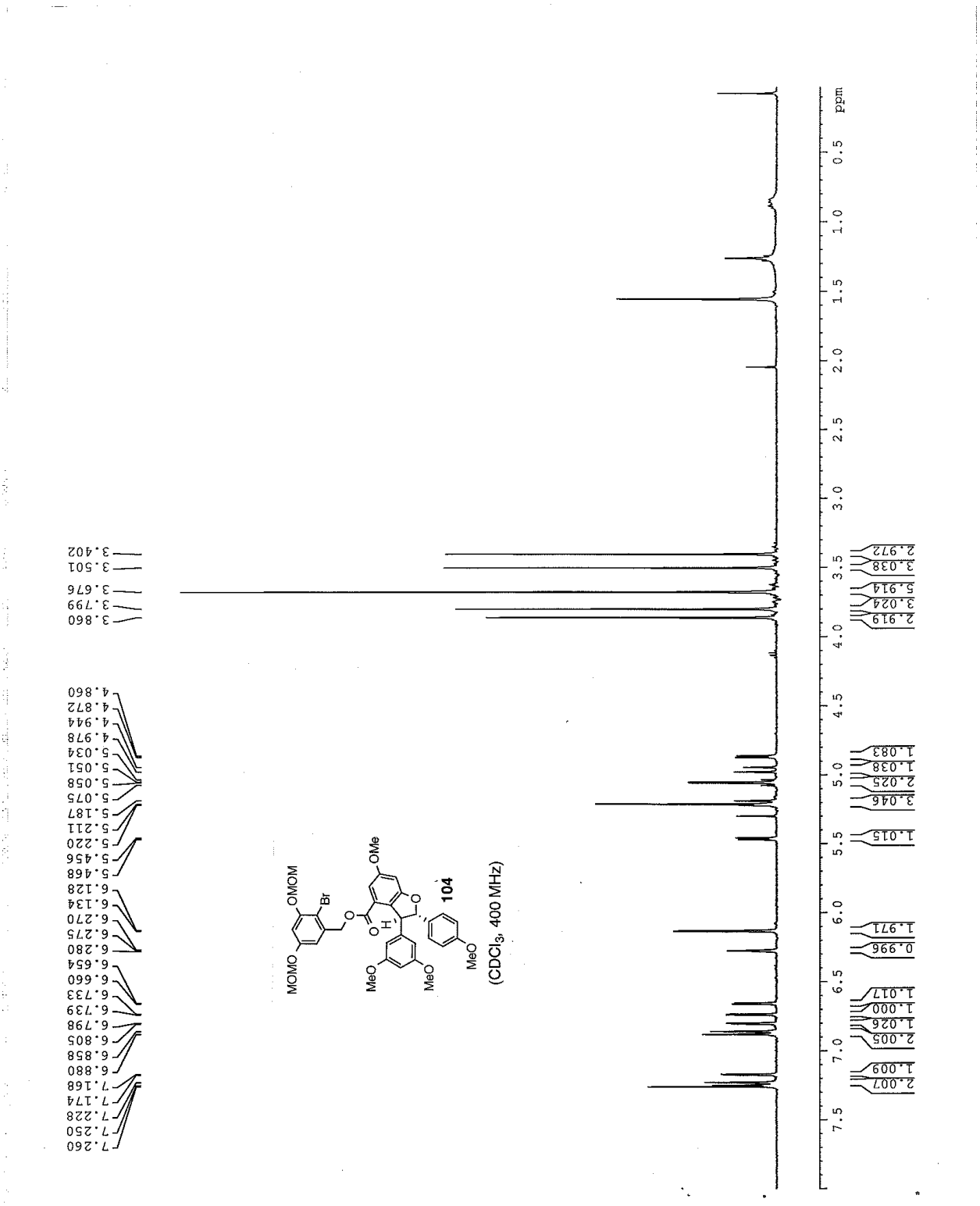

168.784
161.675
161.641
161.243
160.910
159.659
159.330
146.758
142.119
133.844
132.939
127.326
126.960
125.950
120.421
114.145
113.713
108.750
106.068
105.836
101.787
98.796
94.017
93.607
92.346
77.415
77.161
76.907
56.387
55.805
55.477
55.312
55.237
55.205
50.632
88b
(CDCl3, 125 MHz)
ppm

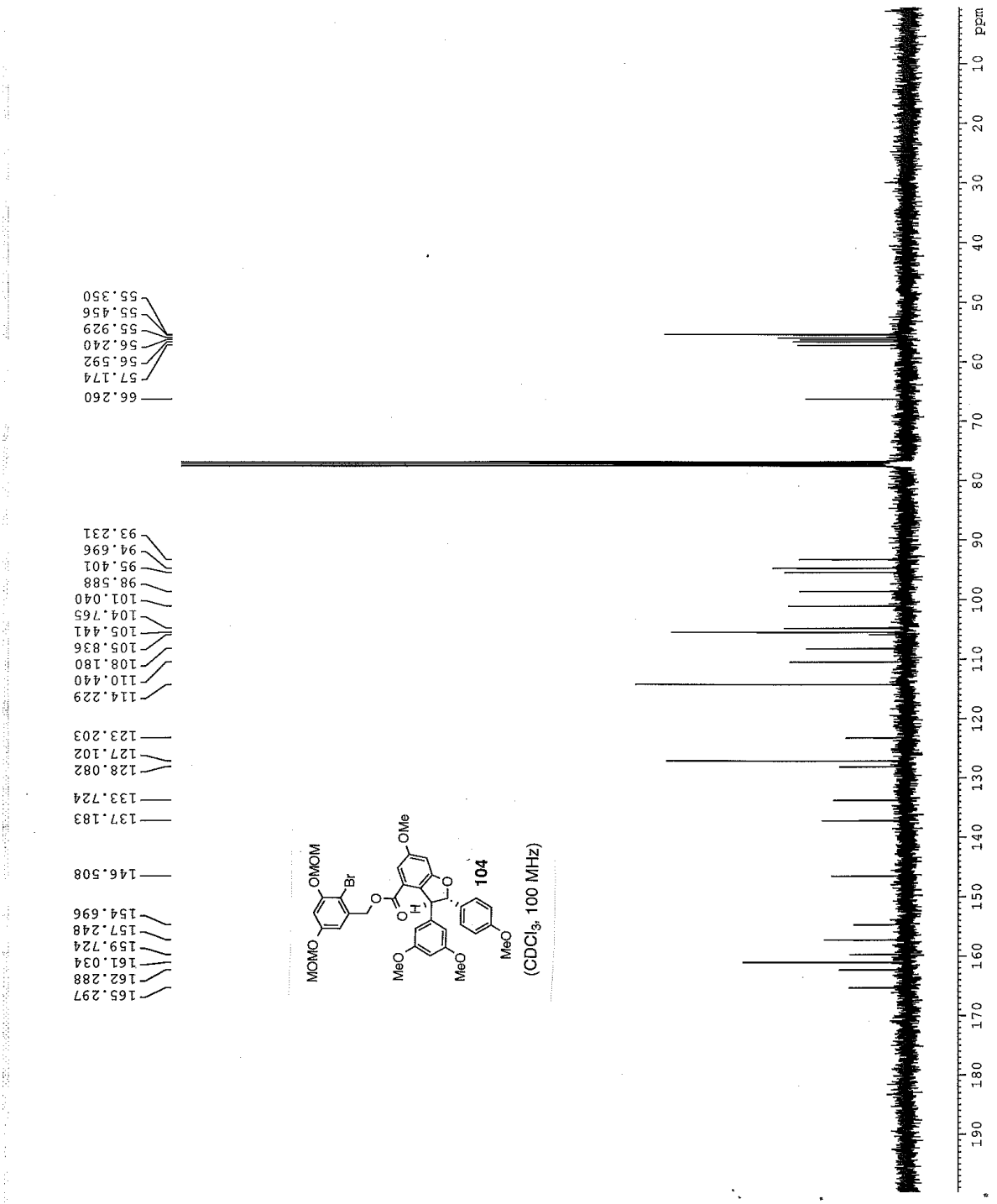

93
(CDCl3, 400 MHz)
MeO
OMe
H
H
ppm

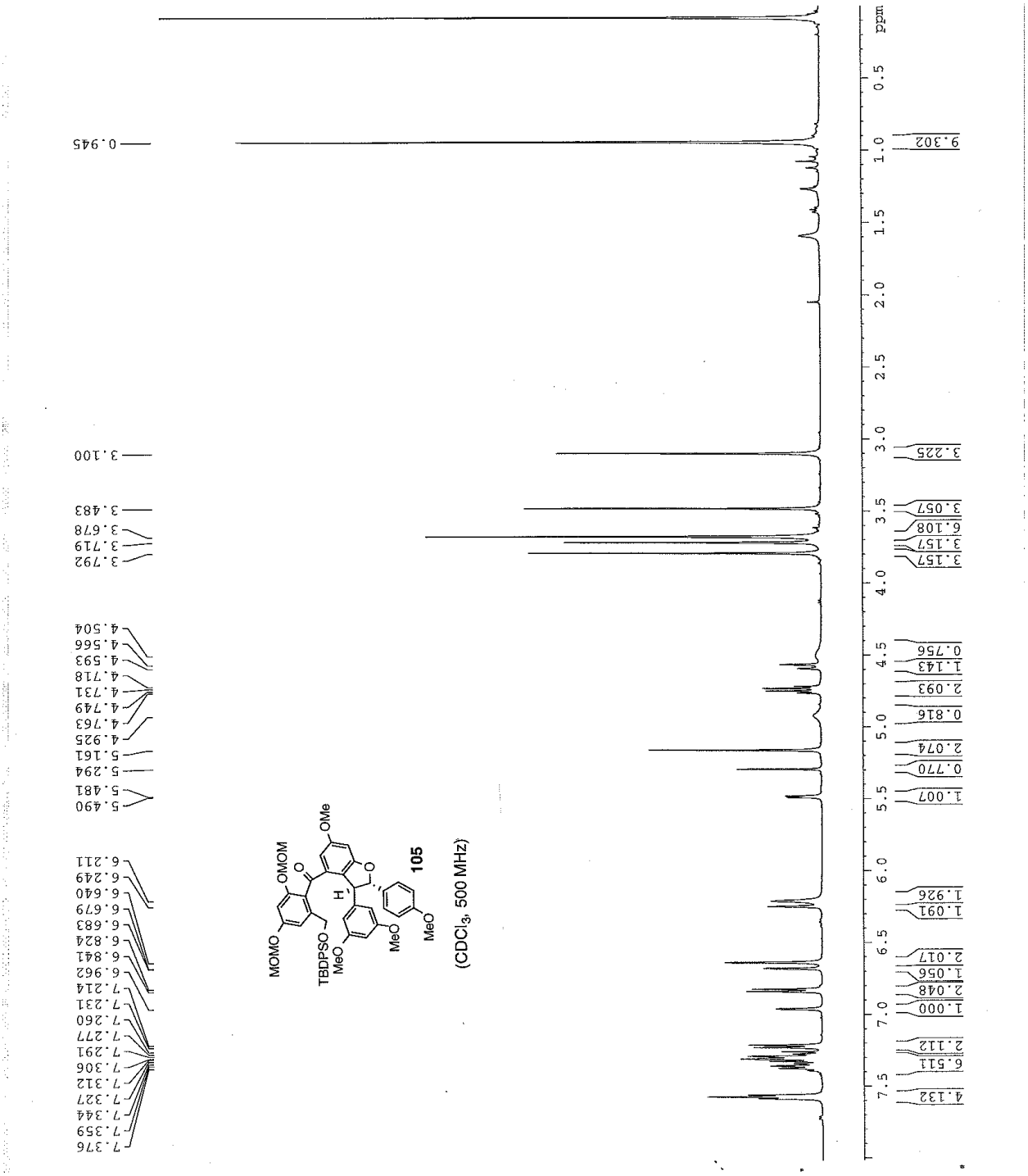

53.641
55.349
55.376
55.472
55.670
55.782
56.345
80.865
81.634
92.910
93.591
94.579
97.678
98.425
106.364
106.627
110.242
114.031
114.110
119.815
120.235
123.377
126.771
128.007
132.368
134.231
139.407
145.177
159.510
159.935
160.759
160.982
161.464
161.568
161.640
OMe
OMe
MeO
MeO
MeO
MeO
MeO
93
(CDCl3, 125 MHz)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
ppm

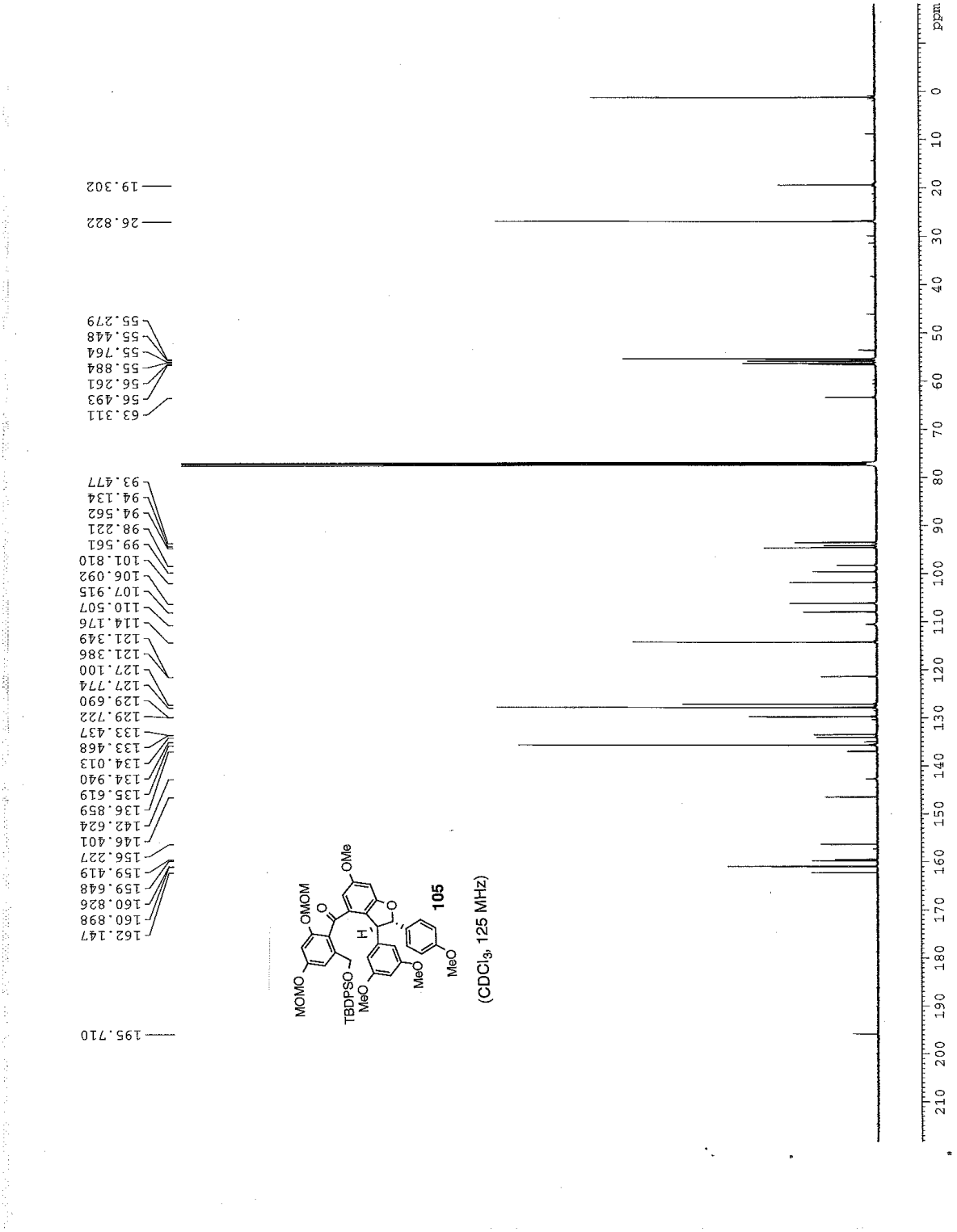

MeO
OMe
MeO
MeO
MeO
OMe
97
(CDCl3, 400 MHz)
ppm

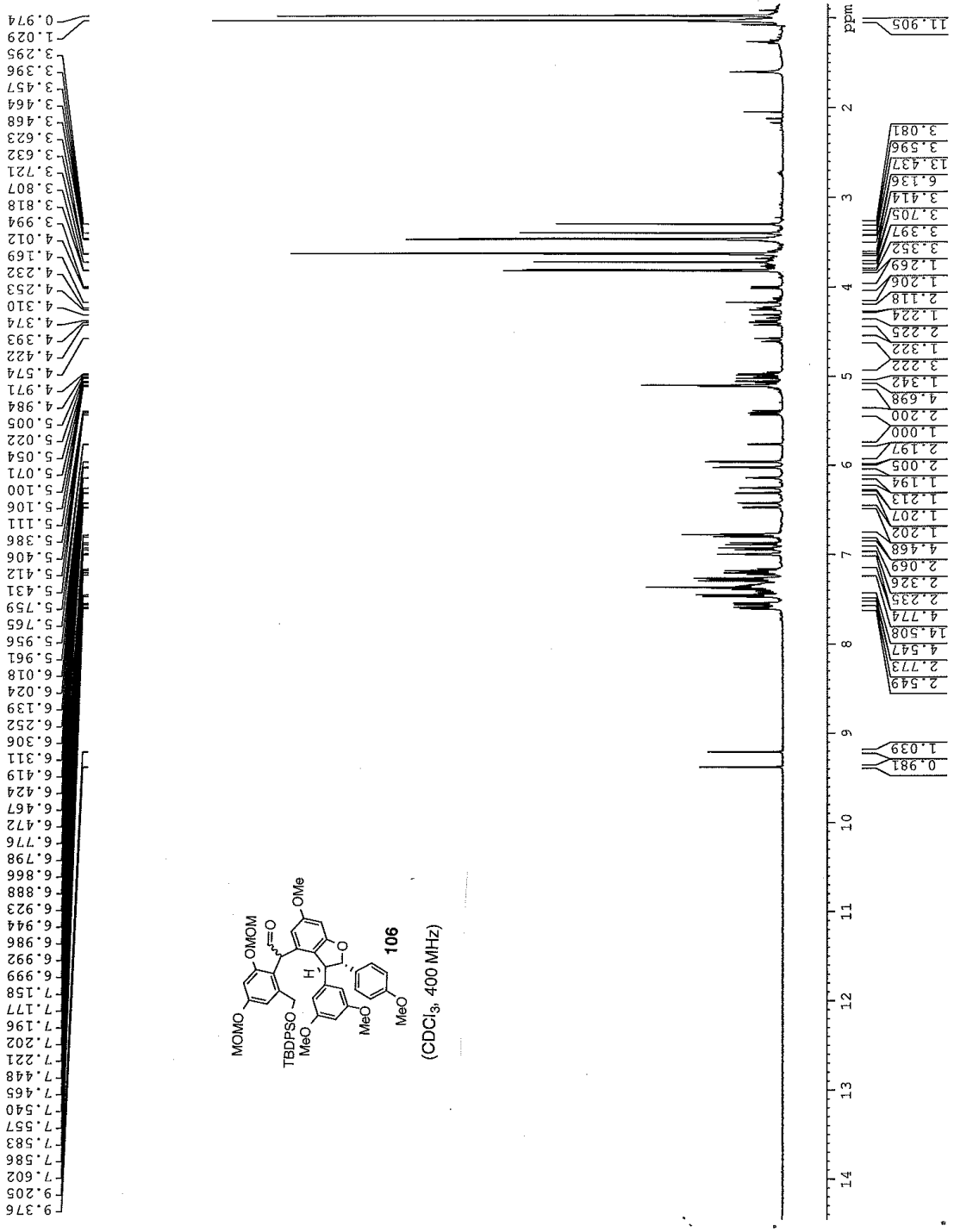

52.947
55.317
55.471
55.657
55.780
55.975
56.596
84.159
91.955
92.134
96.188
98.925
102.508
105.796
113.674
113.748
114.383
117.559
121.063
125.889
126.974
127.478
128.243
133.732
134.021
135.140
138.739
147.835
158.344
158.980
159.350
159.769
160.900
162.189
163.738
MeO
MeO
MeO
MeO
OMe
OMe
H
H
O
O
97
(CDCl3, 125 MHz)
ppm

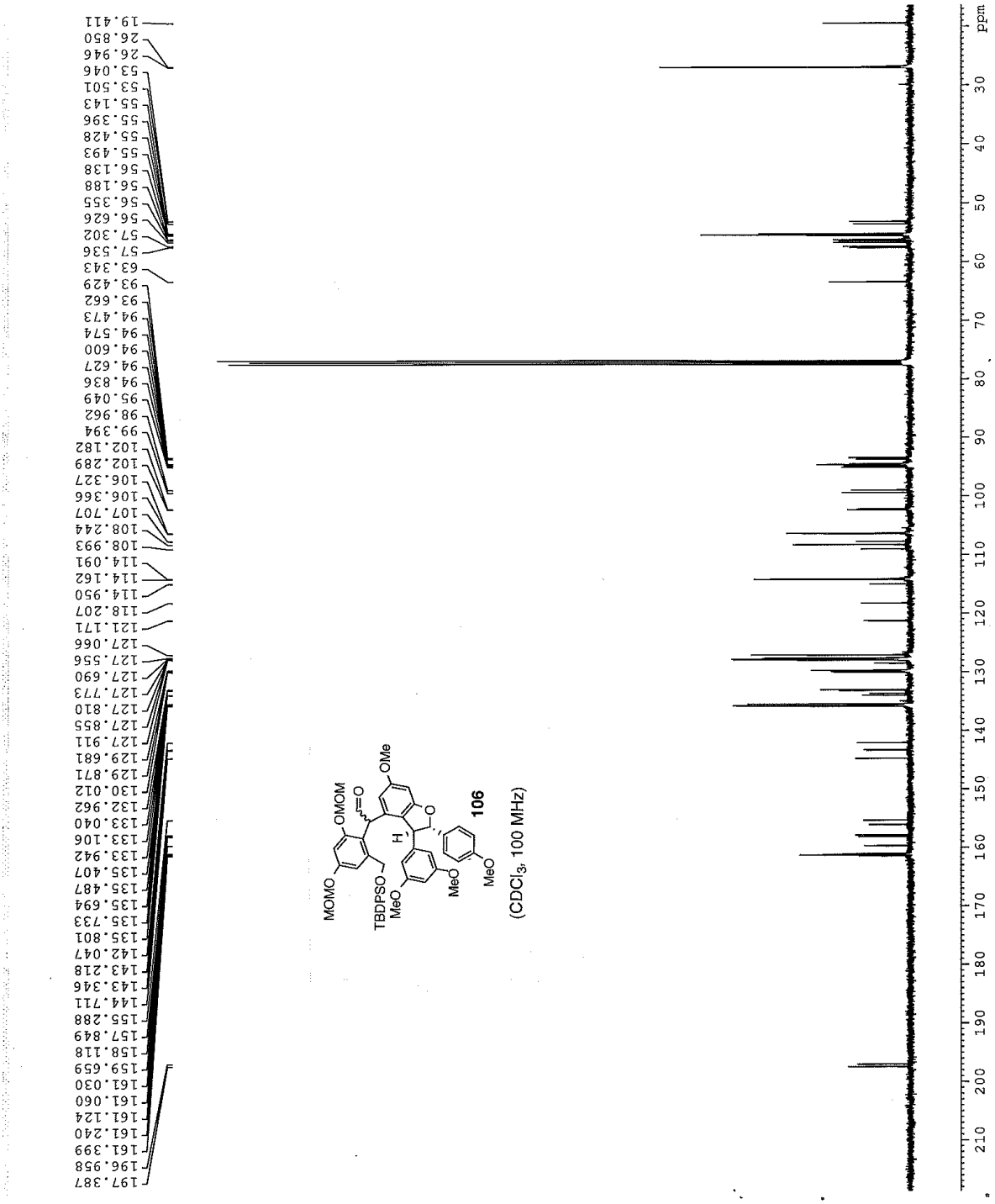

104
(CDCl3, 400 MHz)
MOMO
OMOM
Br
MeO
MeO
MeO
OMe
ppm

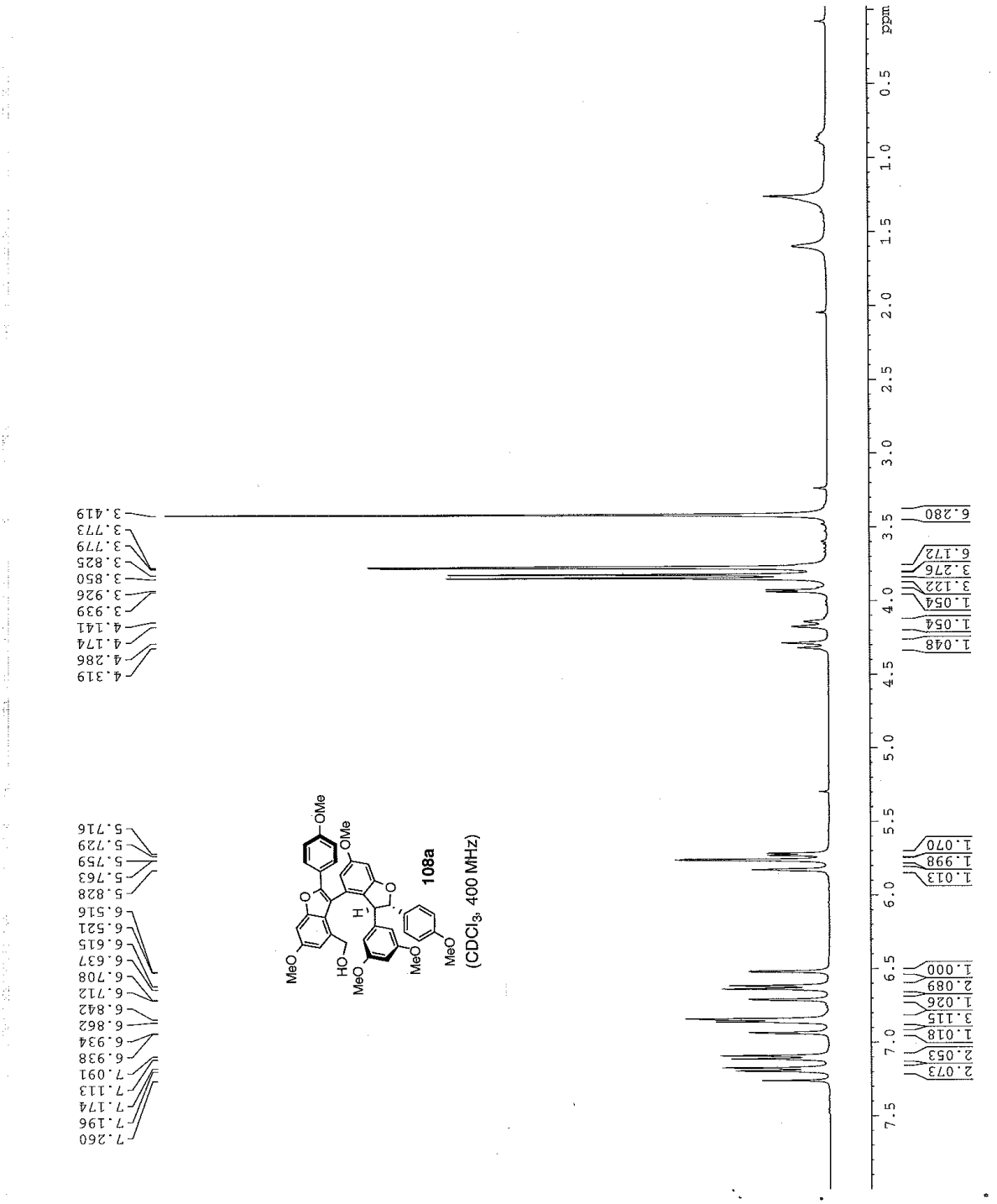

55.350
55.456
55.929
56.240
56.592
57.174
66.260
93.231
94.696
95.401
98.588
101.040
104.765
105.441
105.836
108.180
110.440
114.229
123.203
127.102
128.082
133.724
137.183
146.508
154.696
157.248
159.724
161.034
162.288
165.297
MOMO
OMOM
Br
OMe
MeO
MeO
MeO
104
(CDCl3, 100 MHz)
ppm

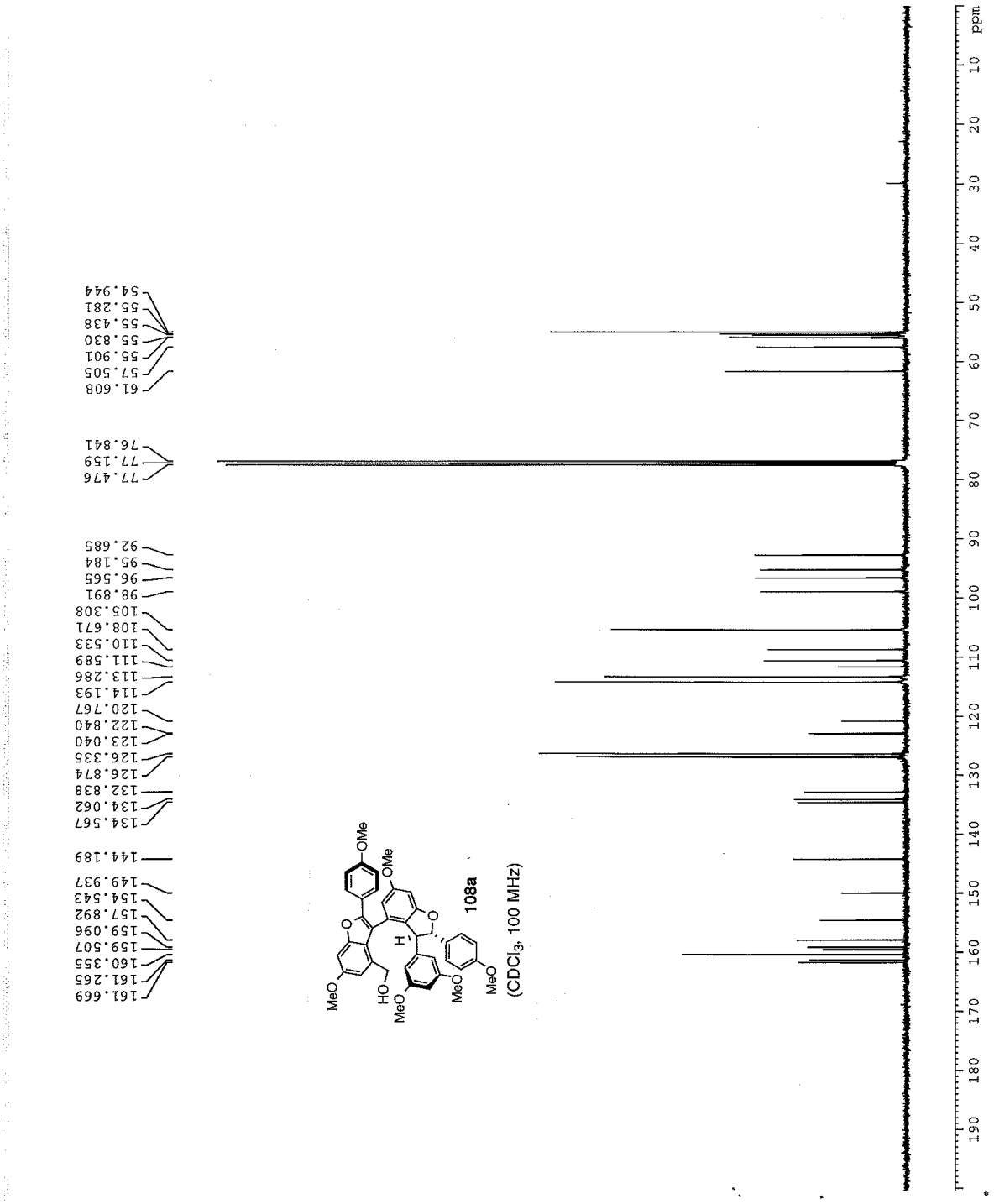

105
(CDCl3, 500 MHz)
MOMO
OMOM
TBDPSO
MeO
OMe
MeO
MeO
ppm

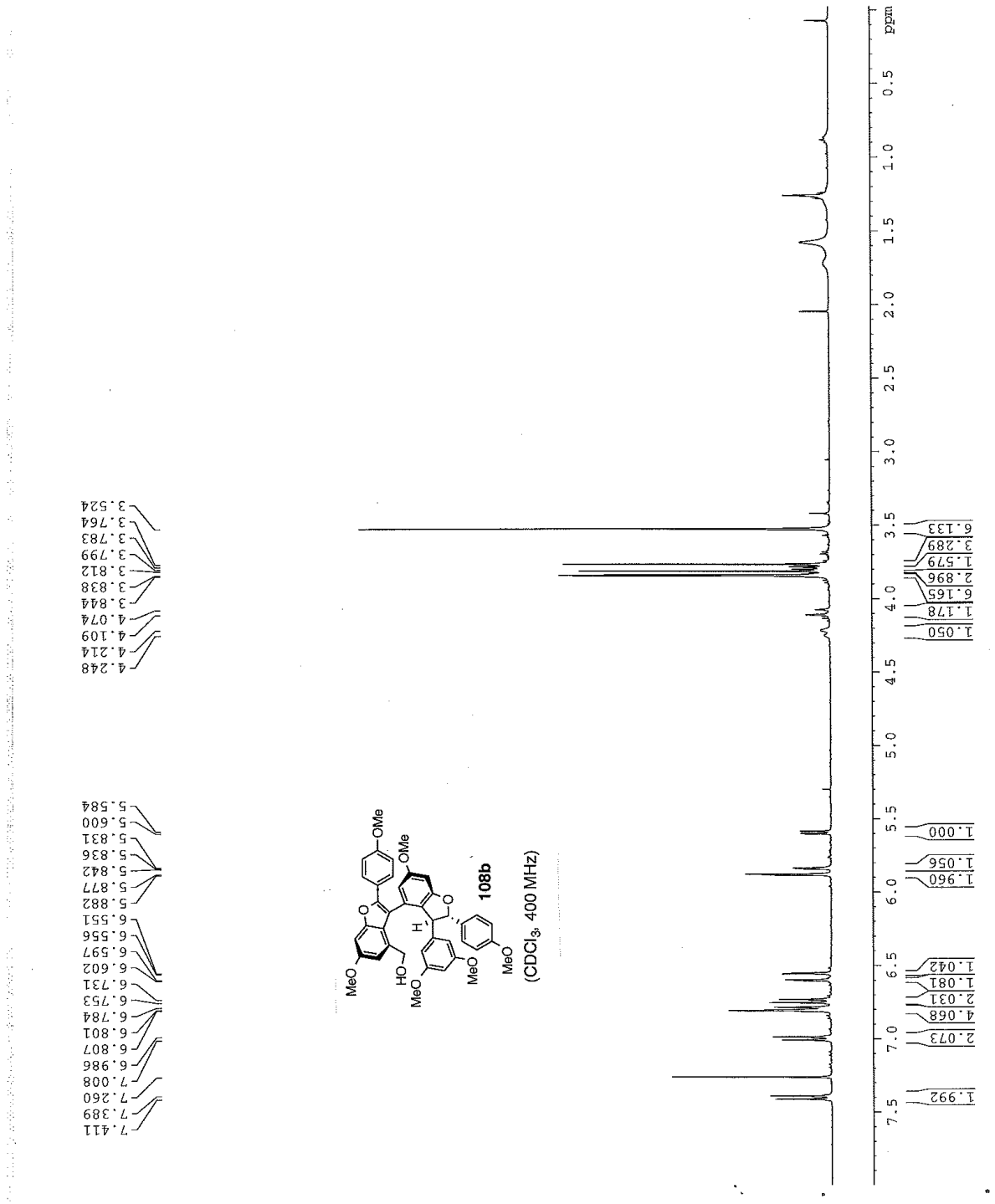

19.302
26.822
55.279
55.448
55.764
55.884
56.261
56.493
63.311
93.477
94.134
94.562
98.221
99.561
101.810
106.092
107.915
110.507
114.176
121.349
121.386
127.100
127.774
129.690
129.722
133.437
133.468
134.013
134.940
135.619
136.859
142.624
146.401
156.227
159.419
159.648
160.826
160.898
162.147
195.710
MOMO
OMOM
TBDPSO
MeO
MeO
MeO
OMe
105
(CDCl3, 125 MHz)
ppm

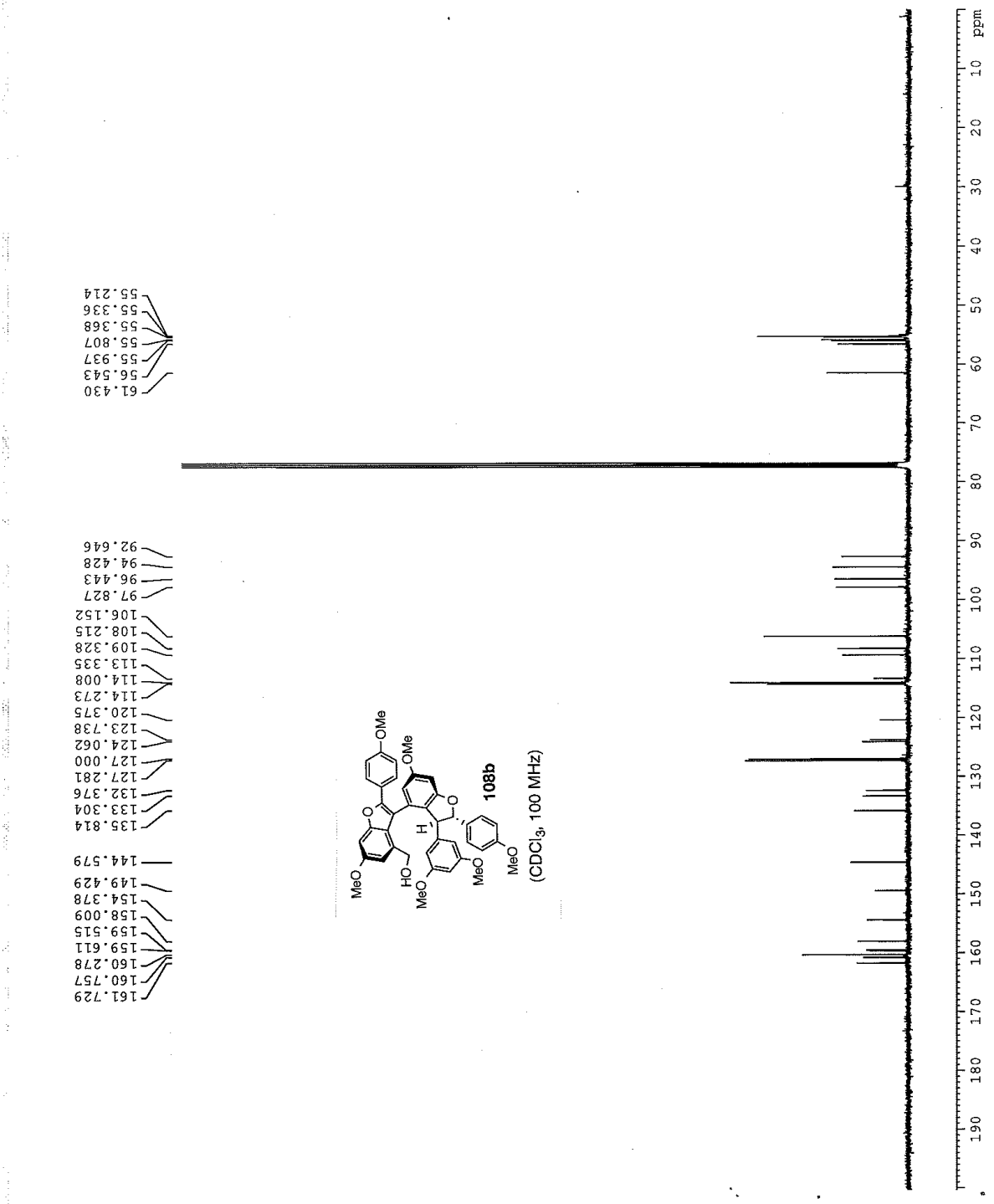

106
(CDCl3, 400 MHz)
ppm

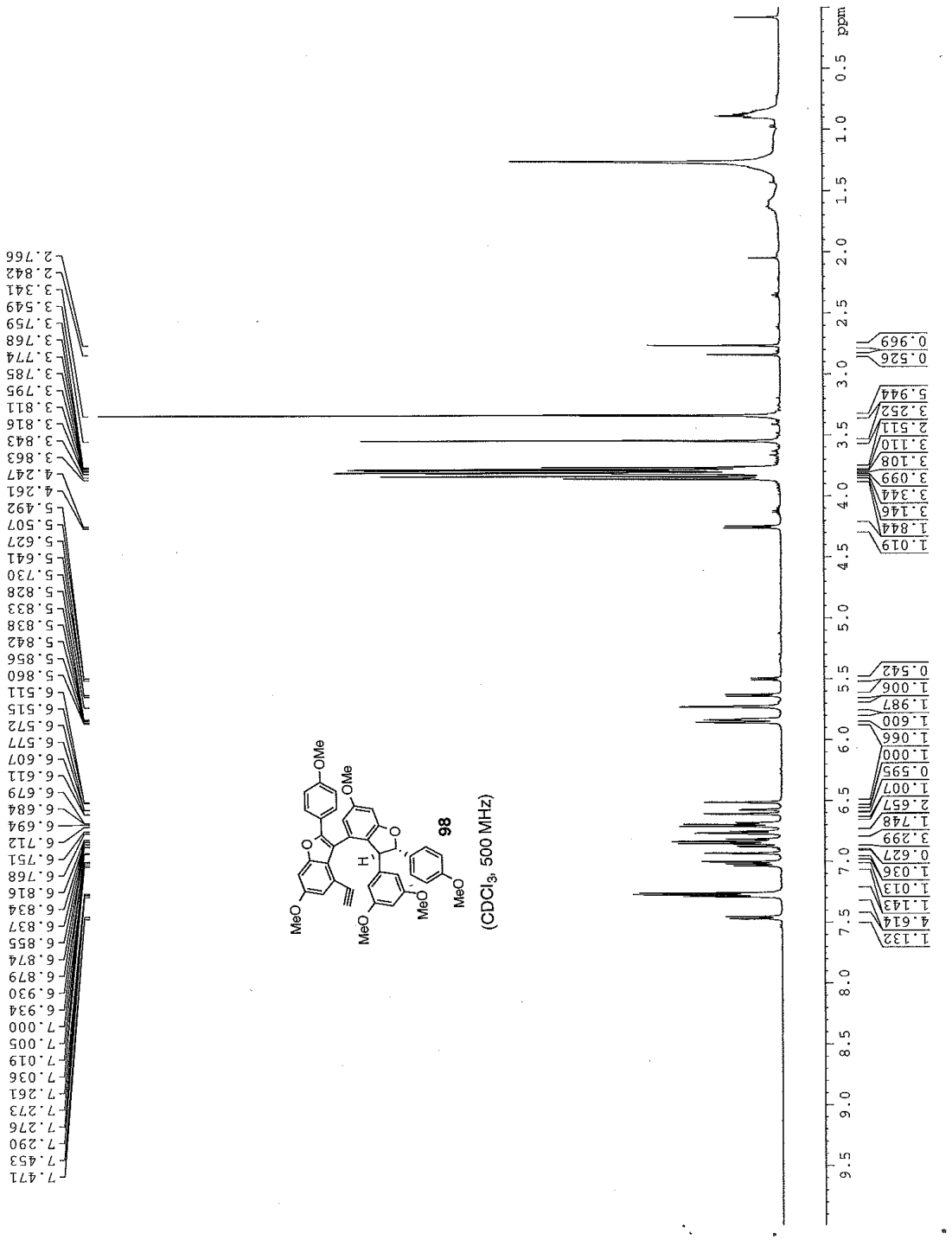

MOMO
OMOM
O
OMe
TBDPSO
MeO
H
O
MeO
MeO
106
(CDCl3, 100 MHz)
ppm

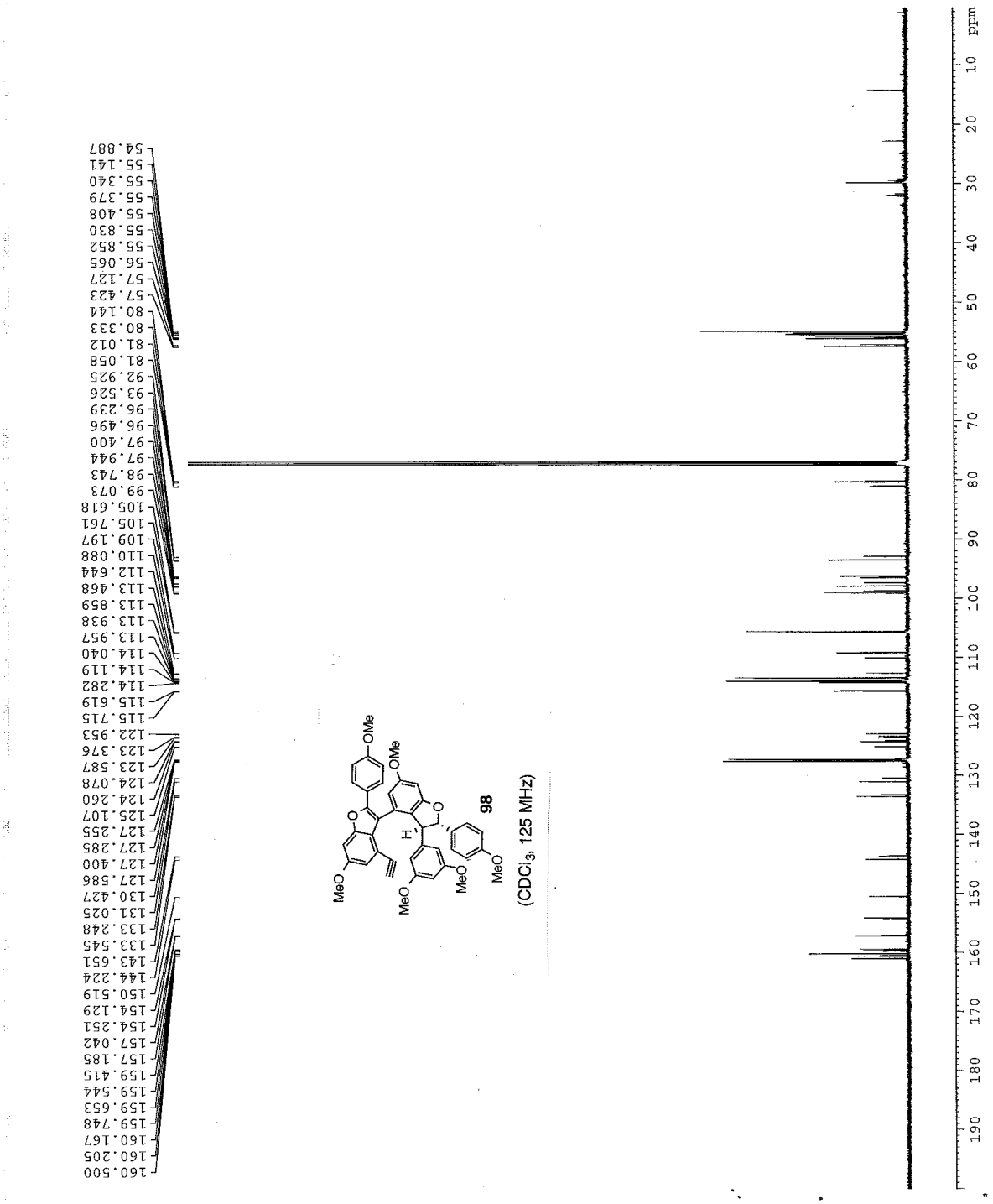

108a
(CDCl3, 400 MHz)
MeO
OMe
H'
ppm

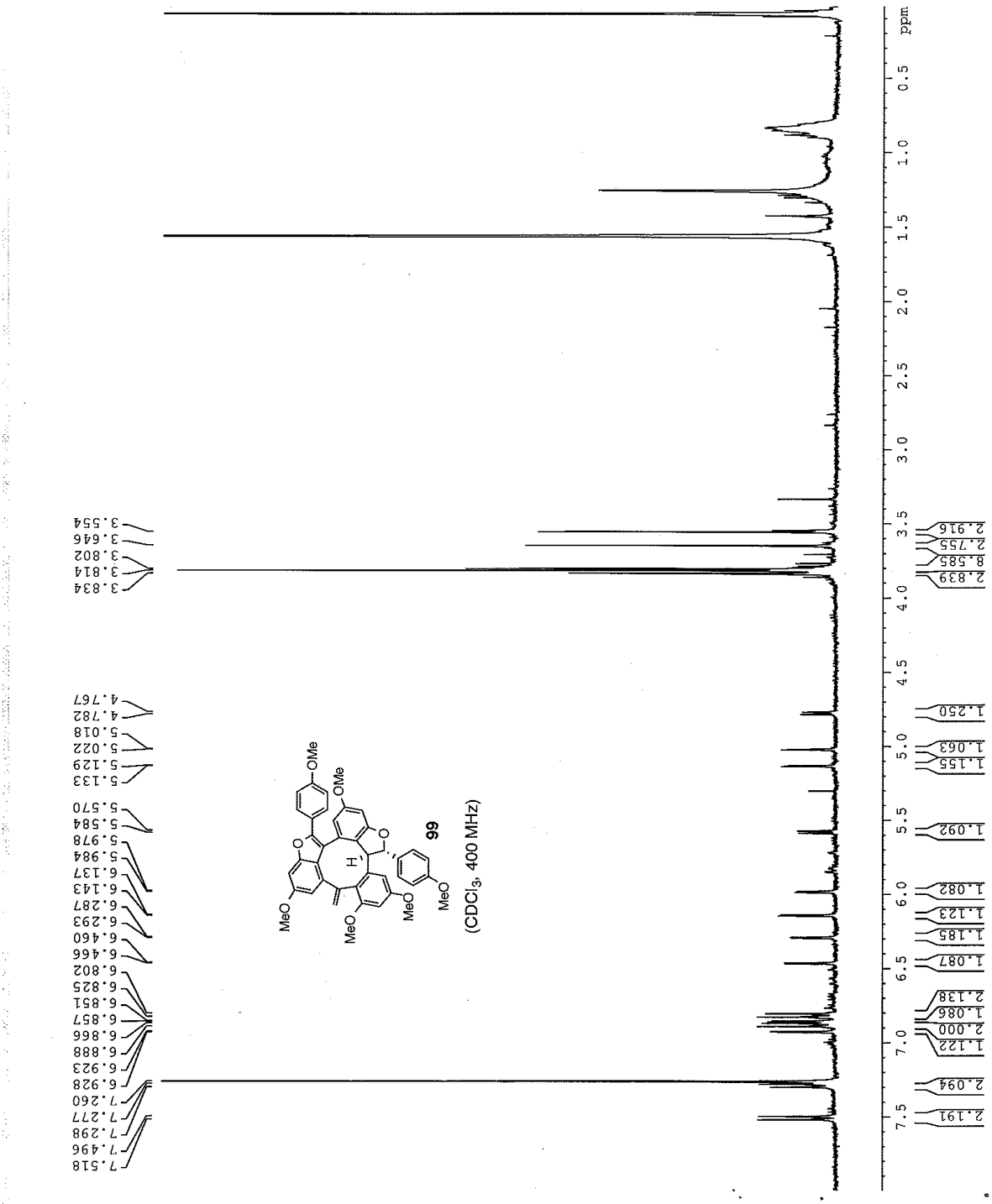

54.944
55.281
55.438
55.830
55.901
57.505
61.608
76.841
77.159
77.476
92.685
95.184
96.565
98.891
105.308
108.671
110.533
111.589
113.286
114.193
120.767
122.840
123.040
126.335
126.874
132.838
134.062
134.567
144.189
149.937
154.543
157.892
159.096
159.507
160.355
161.265
161.669
MeO
OMe
OMe
O
O
H
HO
MeO
MeO
MeO
108a
(CDCl3, 100 MHz)
ppm

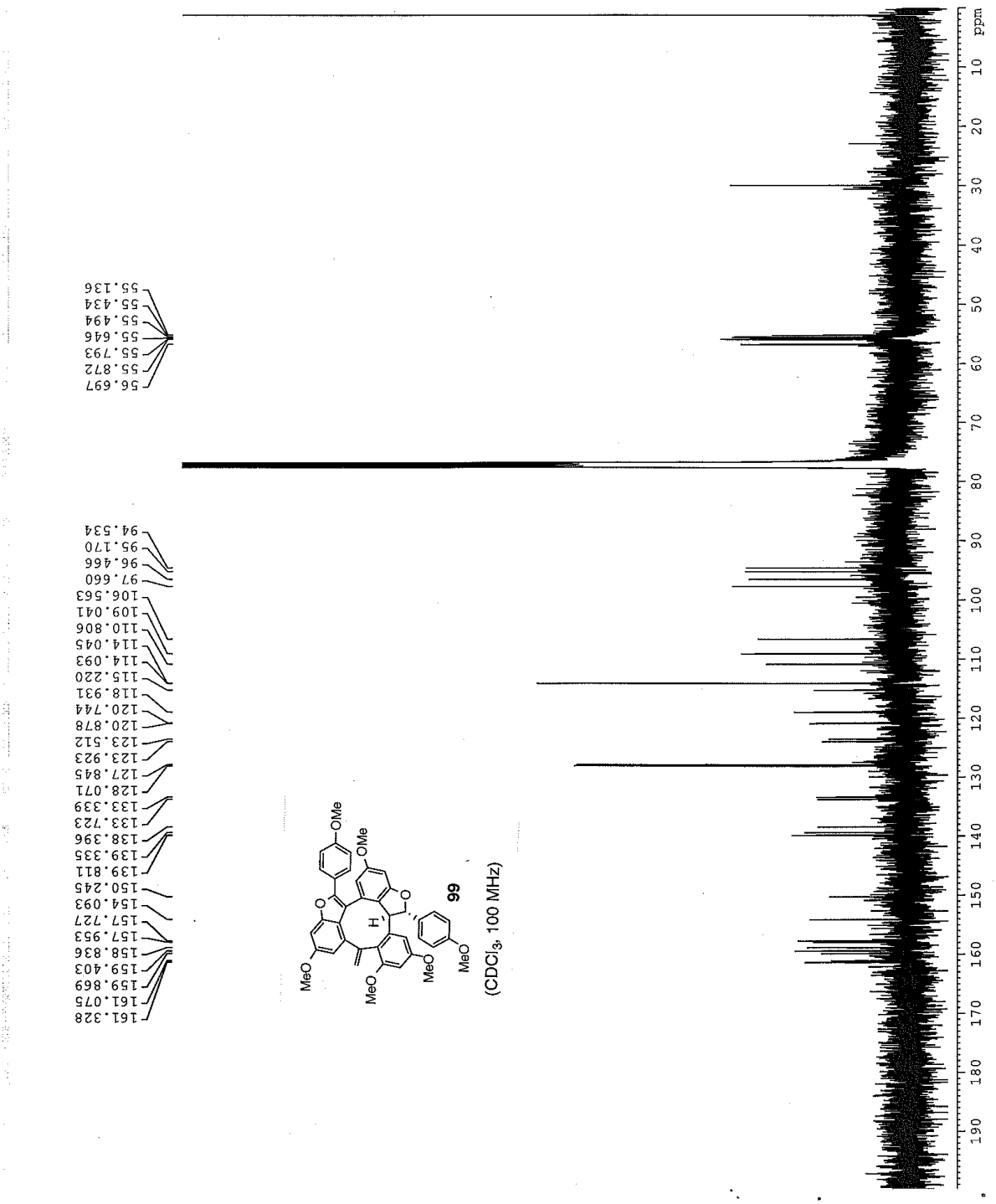

7.411
7.389
7.260
7.008
6.986
6.807
6.801
6.784
6.753
6.731
6.602
6.597
6.556
6.551
5.882
5.877
5.842
5.836
5.831
5.600
5.584
4.248
4.214
4.109
4.074
3.844
3.838
3.812
3.799
3.783
3.764
3.524
OMe
OMe
MeO
HO
MeO
MeO
MeO
H
O
O
108b
(CDCl3, 400 MHz)
1.992
2.073
4.068
2.031
1.081
1.042
1.960
1.056
1.000
1.050
1.178
6.165
2.896
1.579
3.289
6.133
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

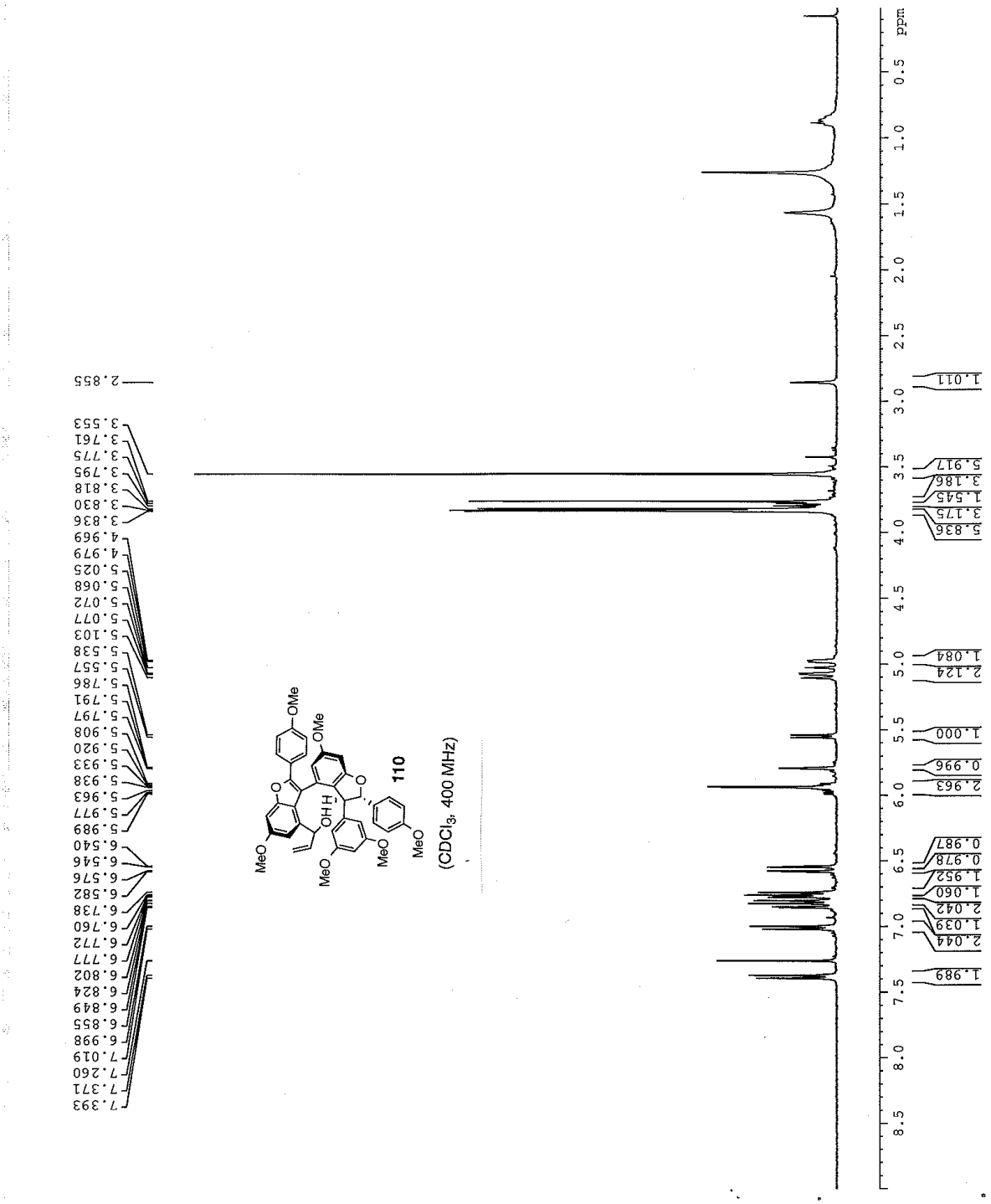

55.214
55.336
55.368
55.807
55.937
56.543
61.430
92.646
94.428
96.443
97.827
106.152
108.215
109.328
113.335
114.008
114.273
120.375
123.738
124.062
127.000
127.281
132.376
133.304
135.814
144.579
149.429
154.378
158.009
159.515
159.611
160.278
160.757
161.729
108b
(CDCl3, 100 MHz)
ppm

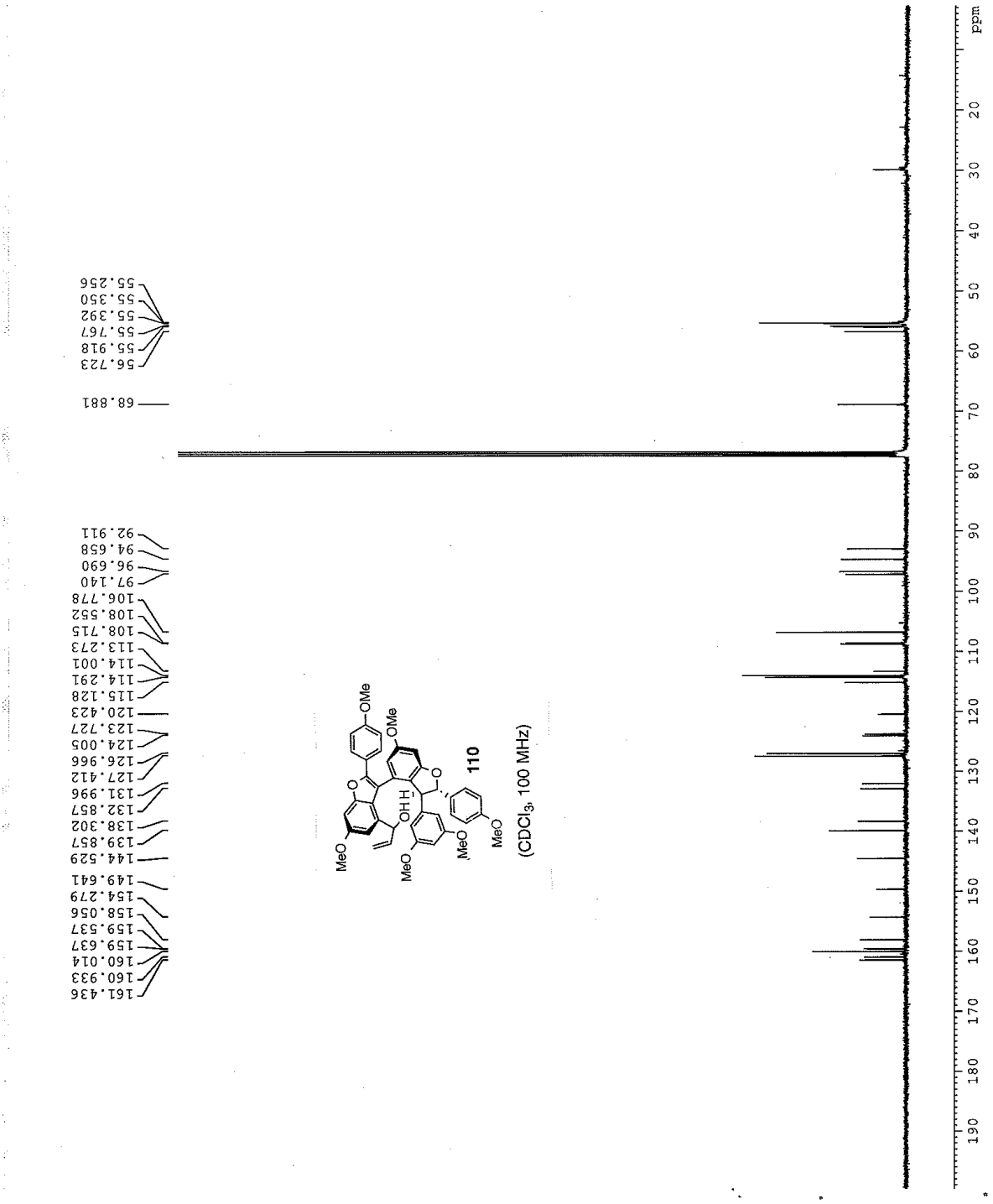

98
(CDCl3, 500 MHz)
ppm

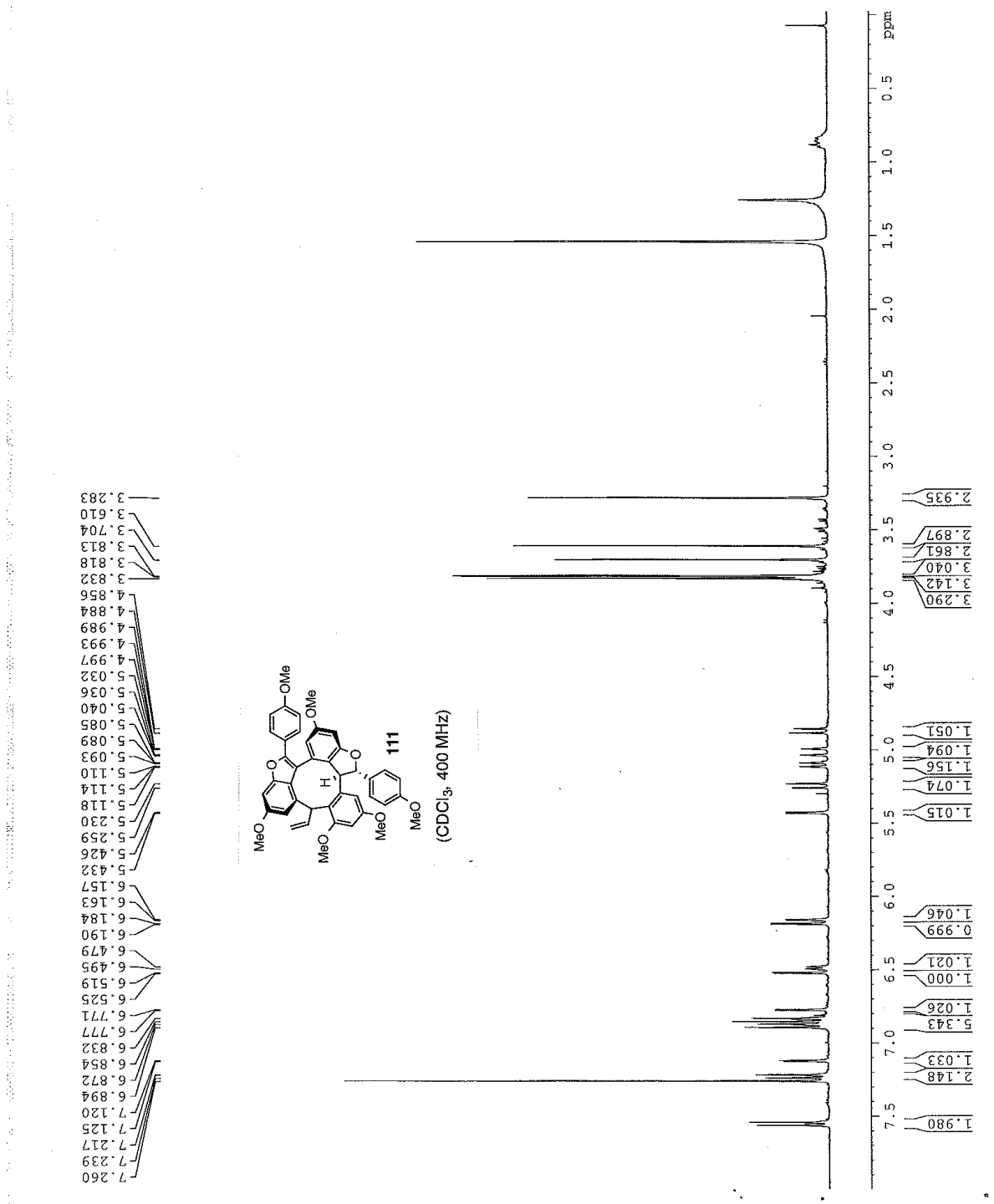

160.500
160.205
160.167
159.748
159.653
159.544
159.415
157.185
157.042
154.251
154.129
150.519
144.224
143.651
133.545
133.248
131.025
130.427
127.586
127.400
127.285
127.255
125.107
124.260
124.078
123.587
123.376
122.953
115.715
115.619
114.282
114.119
114.040
113.957
113.938
113.859
113.468
112.644
110.088
109.197
105.761
105.618
99.073
98.743
97.944
97.400
96.496
96.239
93.526
92.925
81.058
81.012
80.333
80.144
57.423
57.127
56.065
55.852
55.830
55.408
55.379
55.340
55.141
54.887
OMe
OMe
MeO
MeO
MeO
MeO
H
O
O
98
(CDCl3, 125 MHz)
ppm

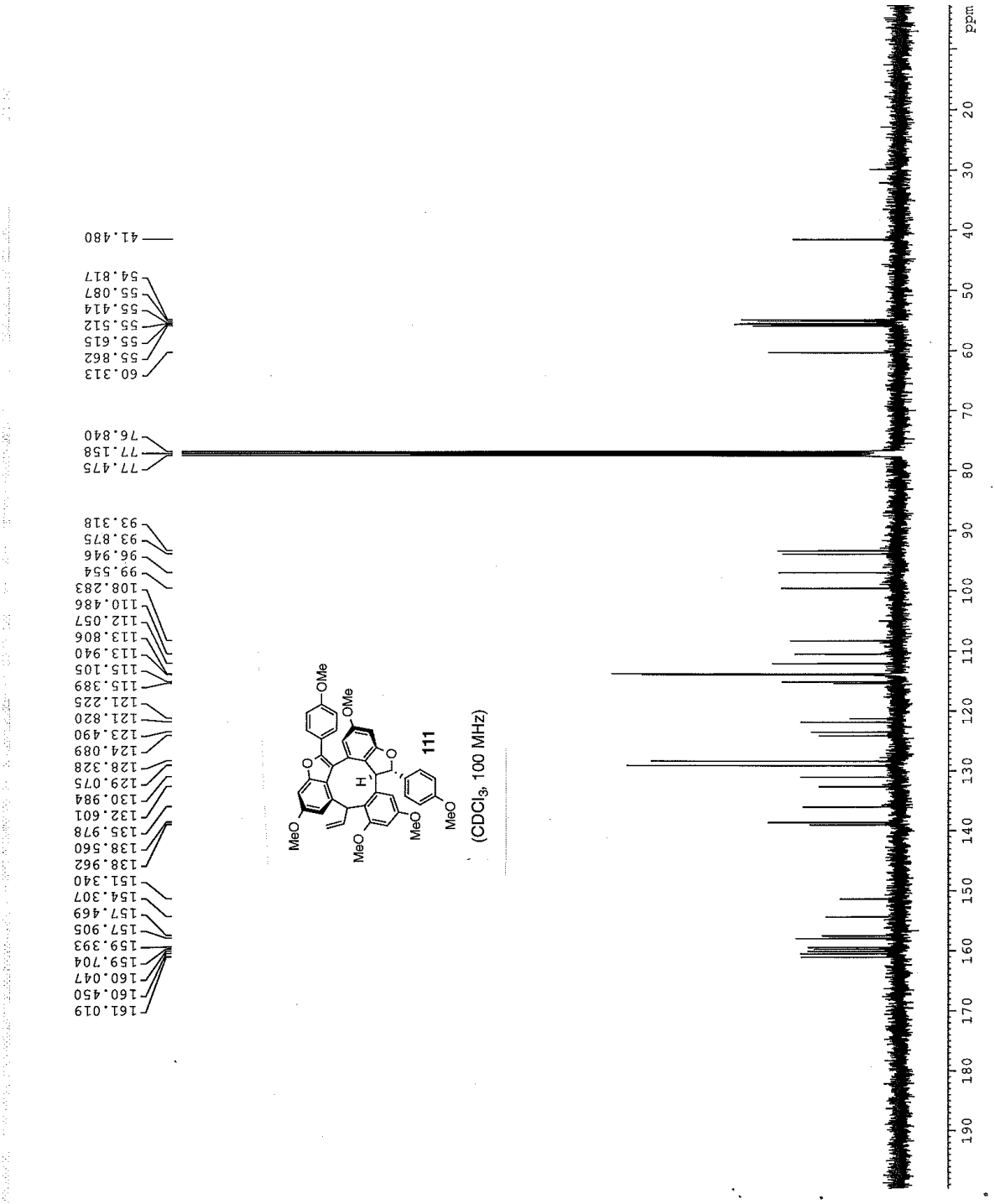

99
(CDCl3, 400 MHz)
MeO
OMe
ppm

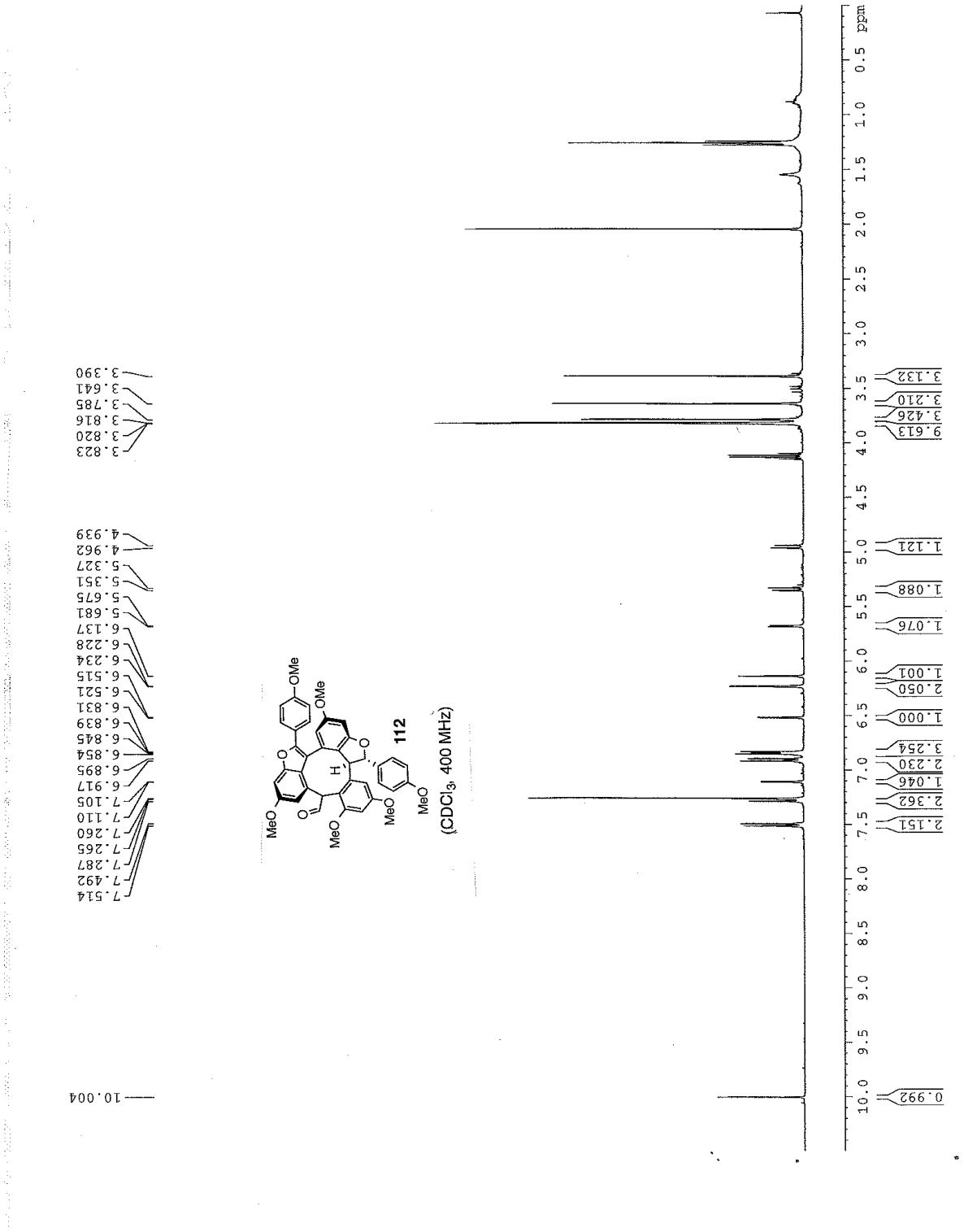

55.136
55.434
55.494
55.646
55.793
55.872
56.697
94.534
95.170
96.466
97.660
106.563
109.041
110.806
114.045
114.093
115.220
118.931
120.744
120.878
123.512
123.923
127.845
128.071
133.339
133.723
138.396
139.335
139.811
150.245
154.093
157.727
157.953
158.836
159.403
159.869
161.075
161.328
MeO
MeO
MeO
MeO
MeO
H
99
(CDCl3, 100 MHz)
ppm

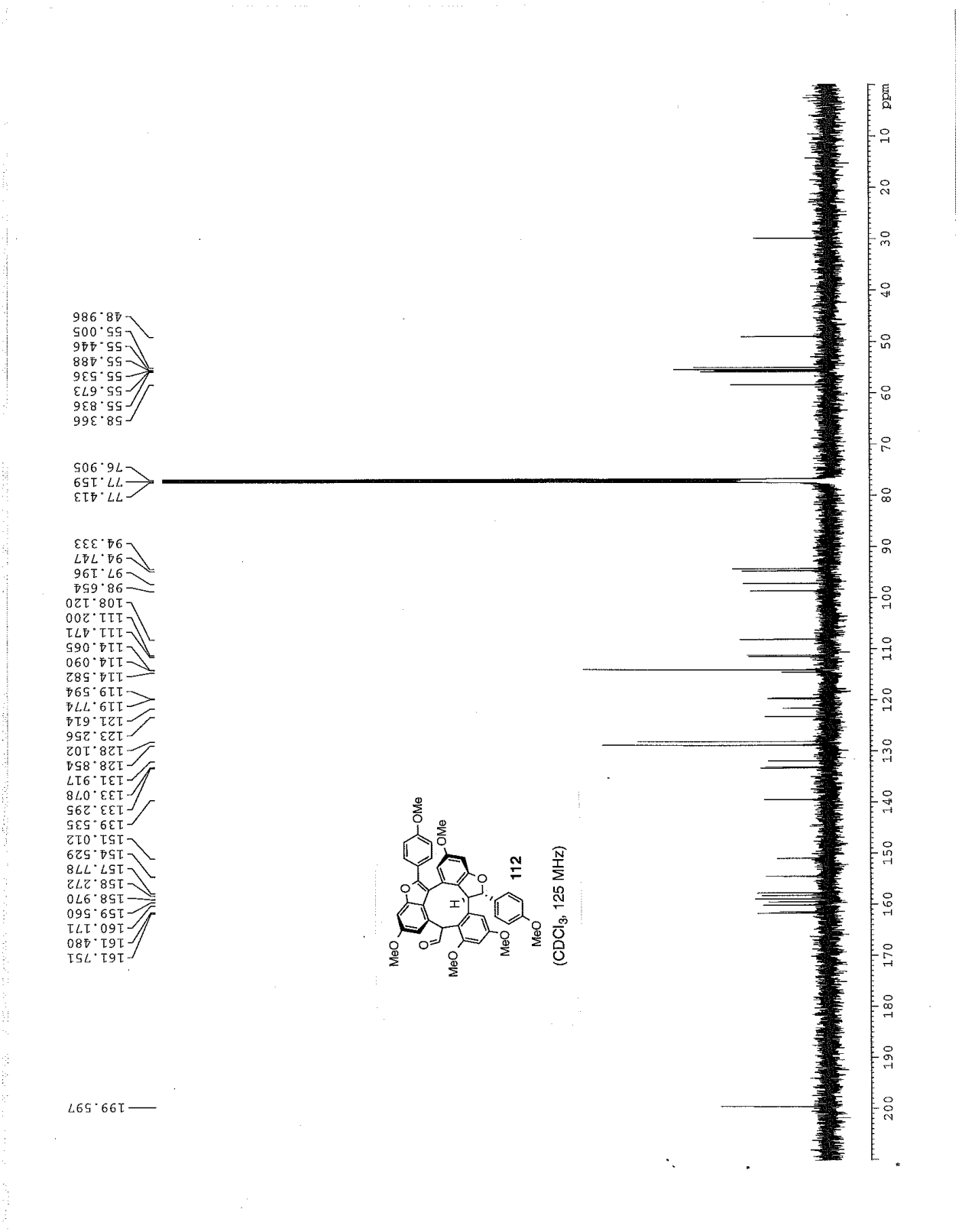

110
(CDCl3, 400 MHz)
MeO
OMe
OMe
OH
H
MeO
MeO
MeO
ppm

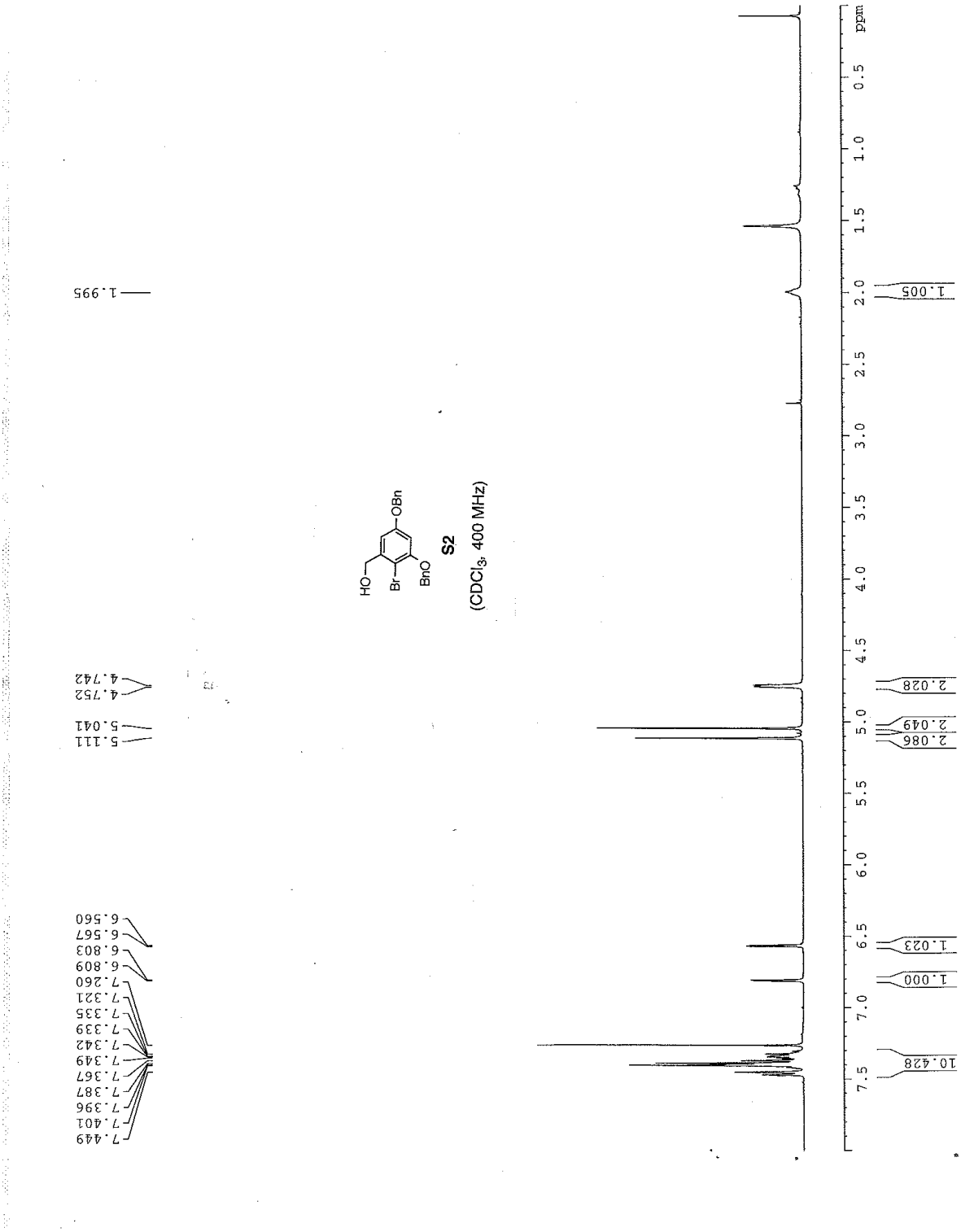

55.256
55.350
55.392
55.767
55.918
56.723
68.881
92.911
94.658
96.690
97.140
106.778
108.552
108.715
113.273
114.001
114.291
115.128
120.423
123.727
124.005
126.966
127.412
131.996
132.857
138.302
139.857
144.529
149.641
154.279
158.056
159.537
159.637
160.014
160.933
161.436
MeO
OMe
OMe
OH
H
O
O
MeO
MeO
MeO
110
(CDCl3, 100 MHz)
ppm

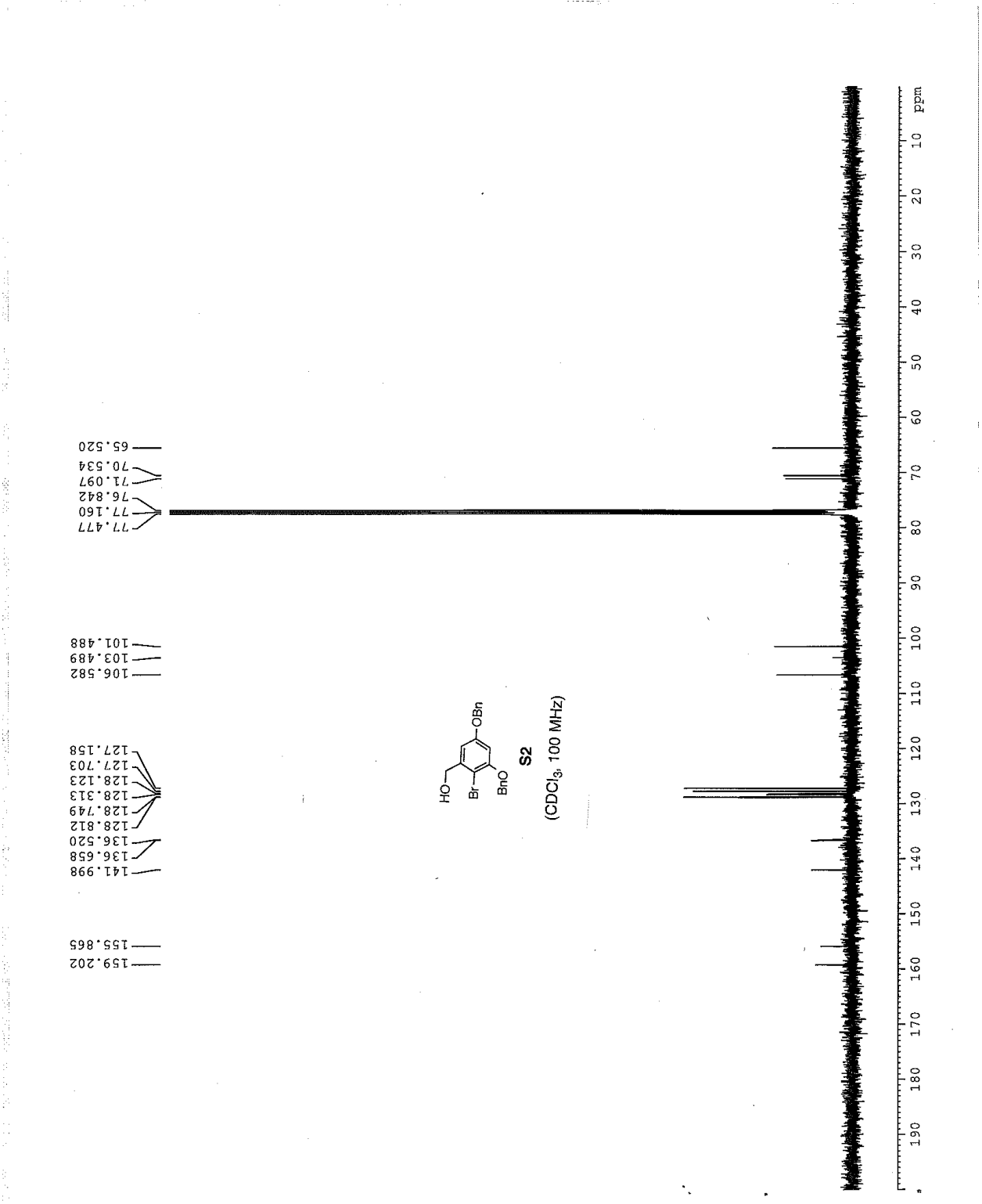

111
(CDCl3, 400 MHz)
MeO
OMe
H
ppm

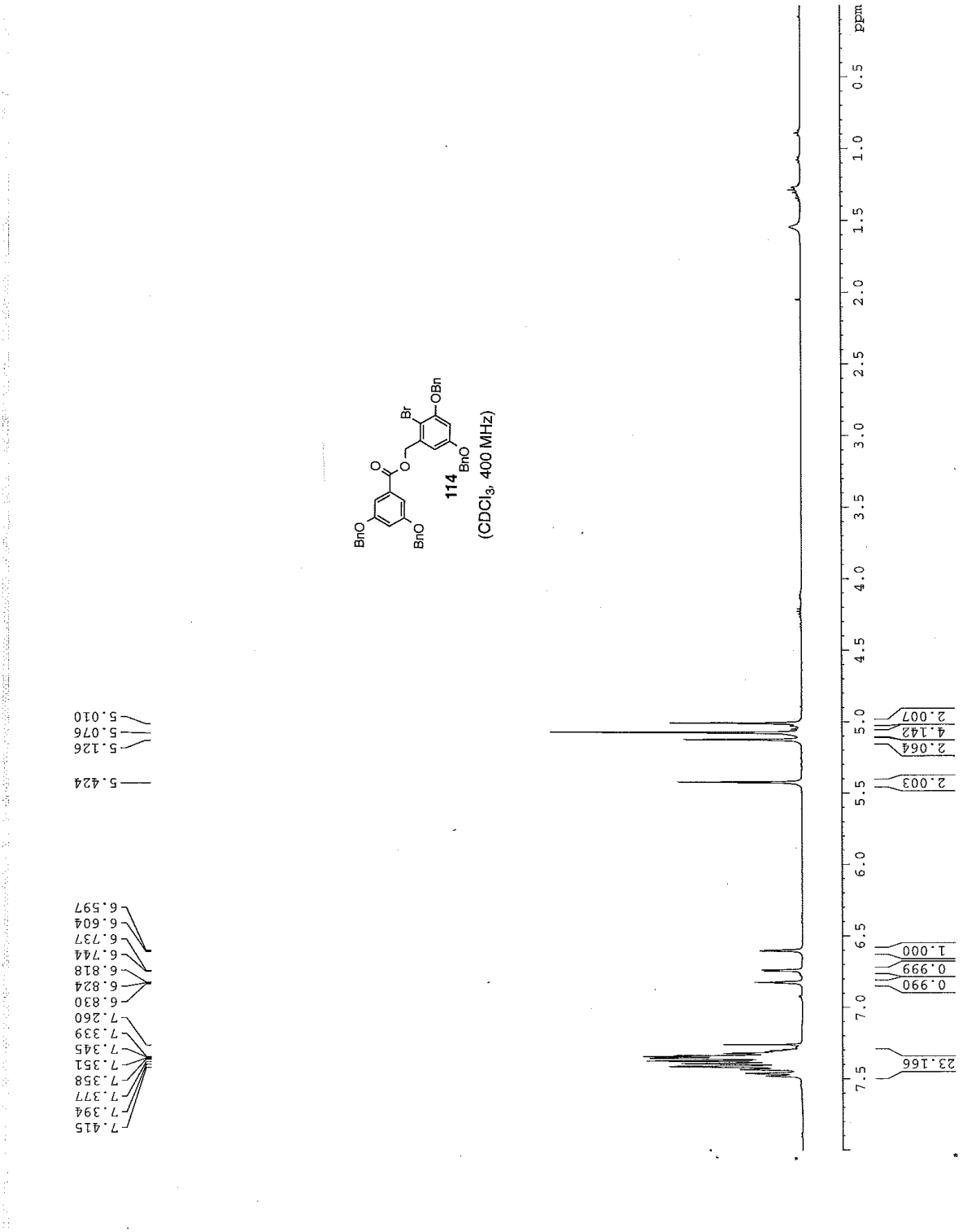

41.480
54.817
55.087
55.414
55.512
55.615
55.862
60.313
76.840
77.158
77.475
93.318
93.875
96.946
99.554
108.283
110.486
112.057
113.806
113.940
115.105
115.389
121.225
121.820
123.490
124.089
128.328
129.075
130.984
132.601
135.978
138.560
138.962
151.340
154.307
157.469
157.905
159.393
159.704
160.047
160.450
161.019
MeO
MeO
MeO
MeO
MeO
OMe
OMe
H
111
(CDCl3, 100 MHz)
ppm

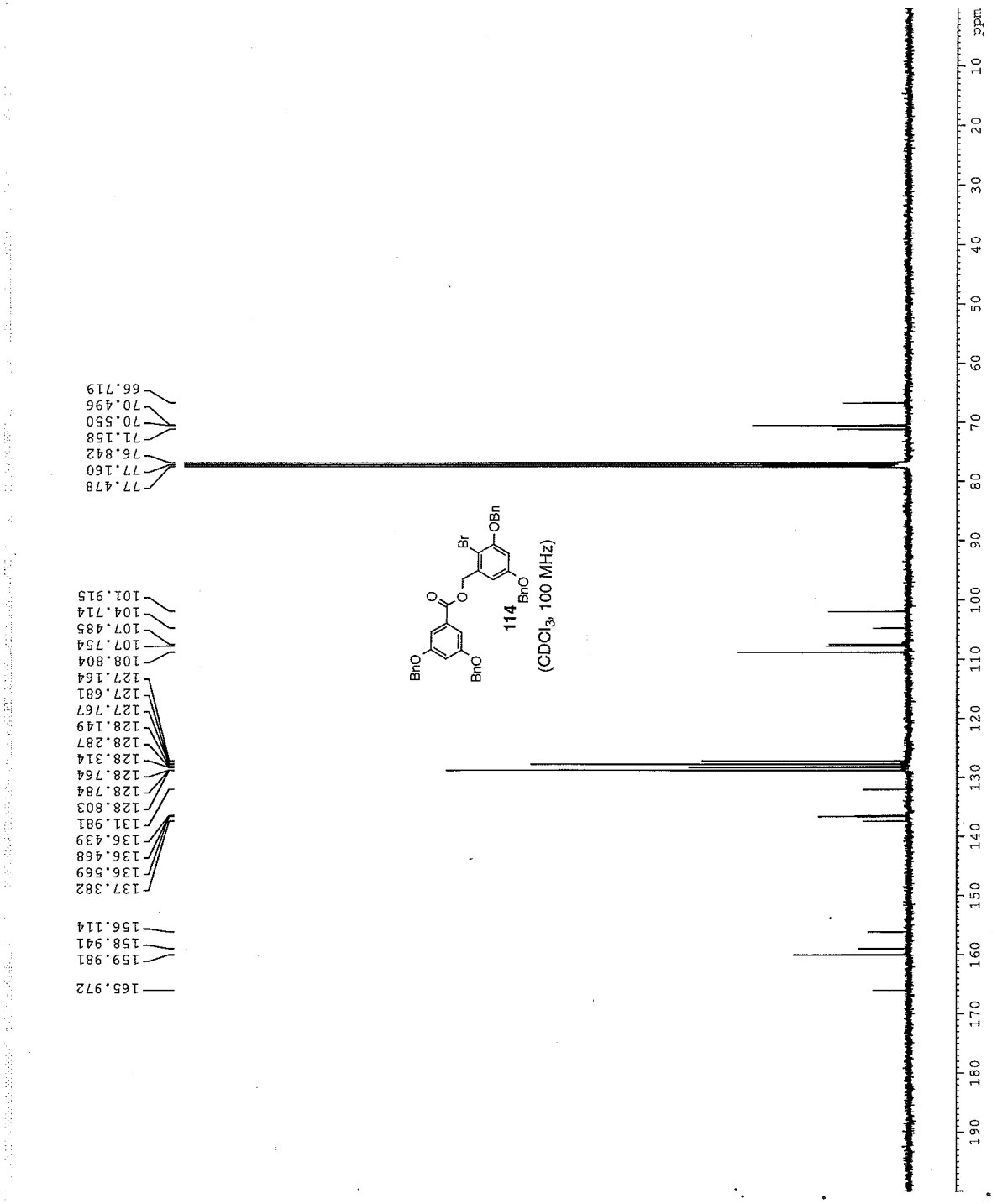

112
(CDCl3, 400 MHz)
MeO
OMe
H
O
10.004
7.514
7.492
7.287
7.265
7.260
7.110
7.105
6.917
6.895
6.854
6.845
6.839
6.831
6.521
6.515
6.234
6.228
6.137
5.681
5.675
5.351
5.327
4.962
4.939
3.823
3.820
3.816
3.785
3.641
3.390
0.992
2.151
2.362
1.046
2.230
3.254
1.000
2.050
1.001
1.076
1.088
1.121
9.613
3.426
3.210
3.132
ppm

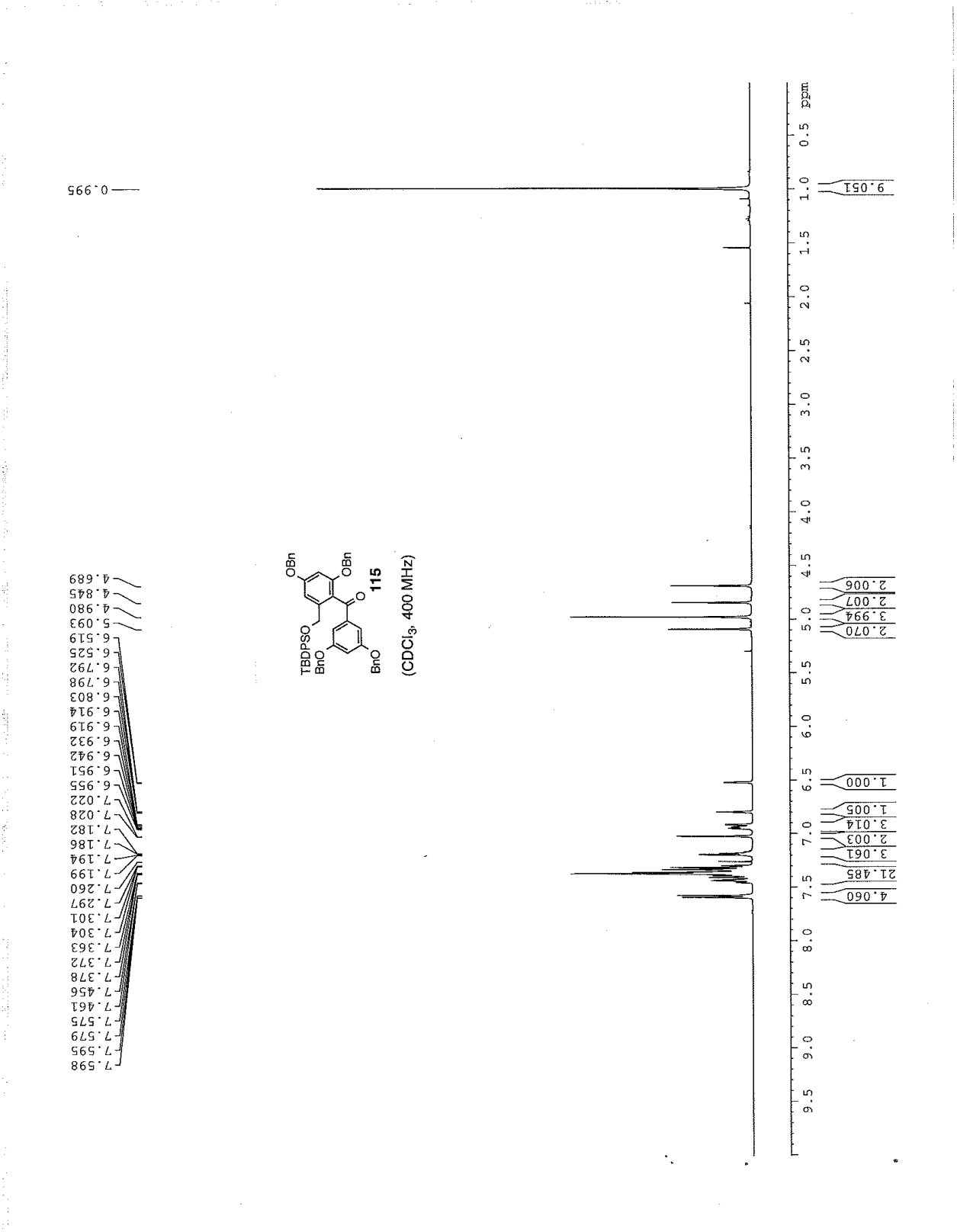

199.597
161.751
161.480
160.171
159.560
158.970
158.272
157.778
154.529
151.012
139.535
133.295
133.078
131.917
128.854
128.102
123.256
121.614
119.774
119.594
114.582
114.090
114.065
111.471
111.200
108.120
98.654
97.196
94.747
94.333
77.413
77.159
76.905
58.366
55.836
55.673
55.536
55.488
55.446
55.005
48.986
ppm
OMe
OMe
MeO
MeO
MeO
MeO
112
(CDCl3, 125 MHz)

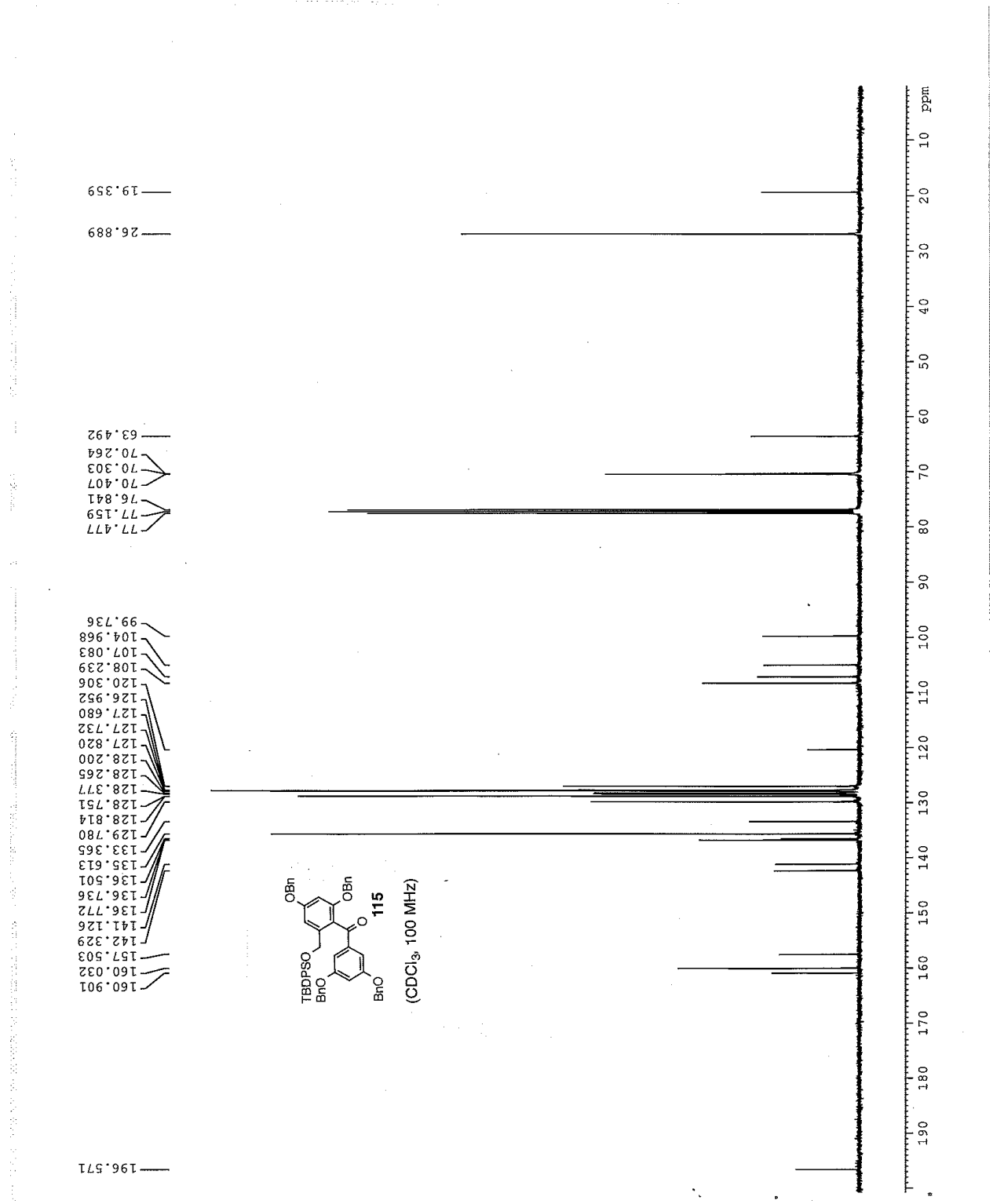

HO
Br
BnO
OBn
S2
(CDCl3, 400 MHz)
ppm
10.428
1.023
1.000
2.028
2.049
2.086
1.005
1.995
7.449
7.401
7.396
7.387
7.367
7.349
7.342
7.339
7.335
7.321
7.260
6.809
6.803
6.567
6.560
5.111
5.041
4.752
4.742

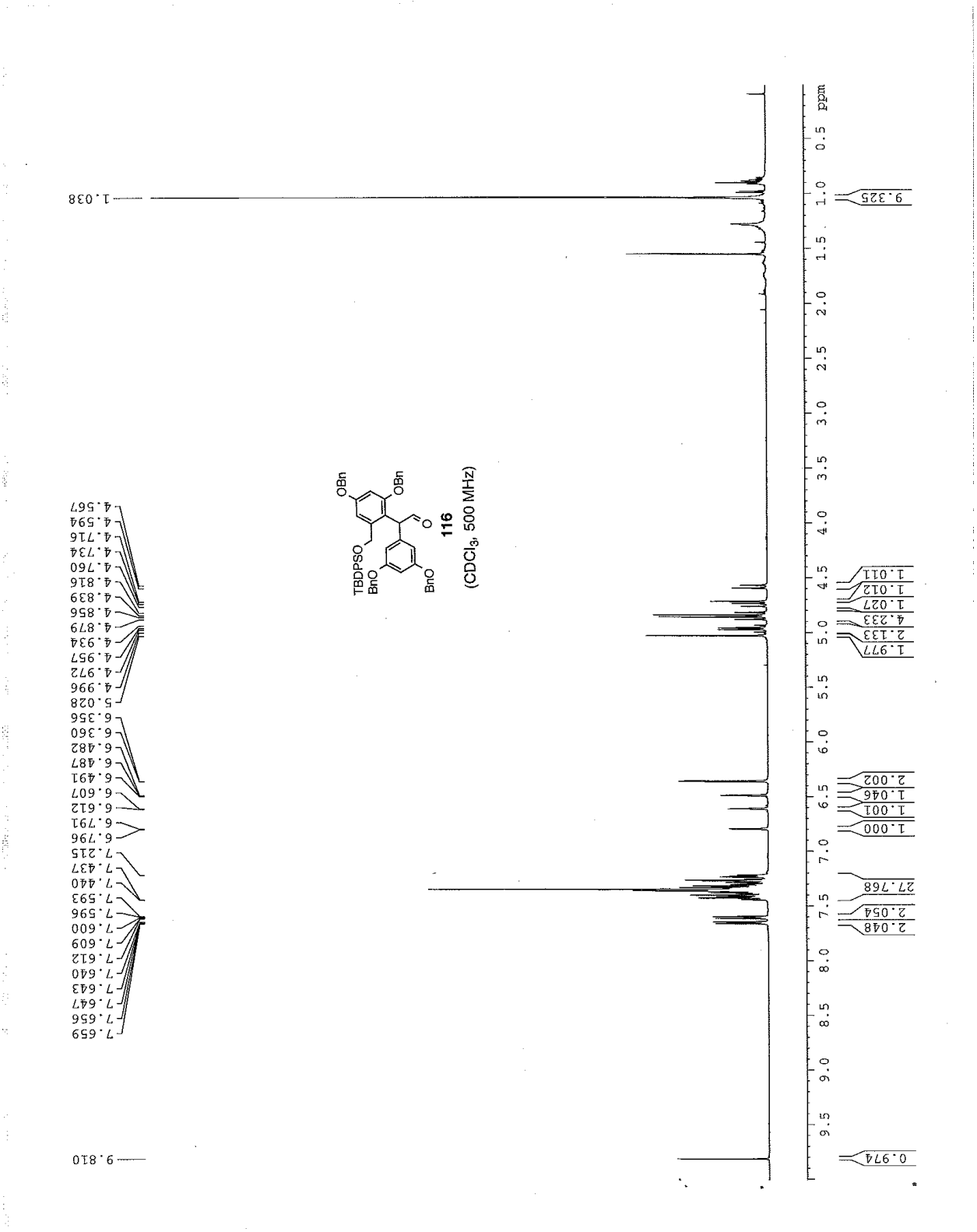

65.520
70.534
71.097
76.842
77.160
77.477
101.488
103.489
106.582
127.158
127.703
128.123
128.313
128.749
128.812
136.520
136.658
141.998
155.865
159.202
OBn
HO
Br
BnO
S2
(CDCl3, 100 MHz)
ppm

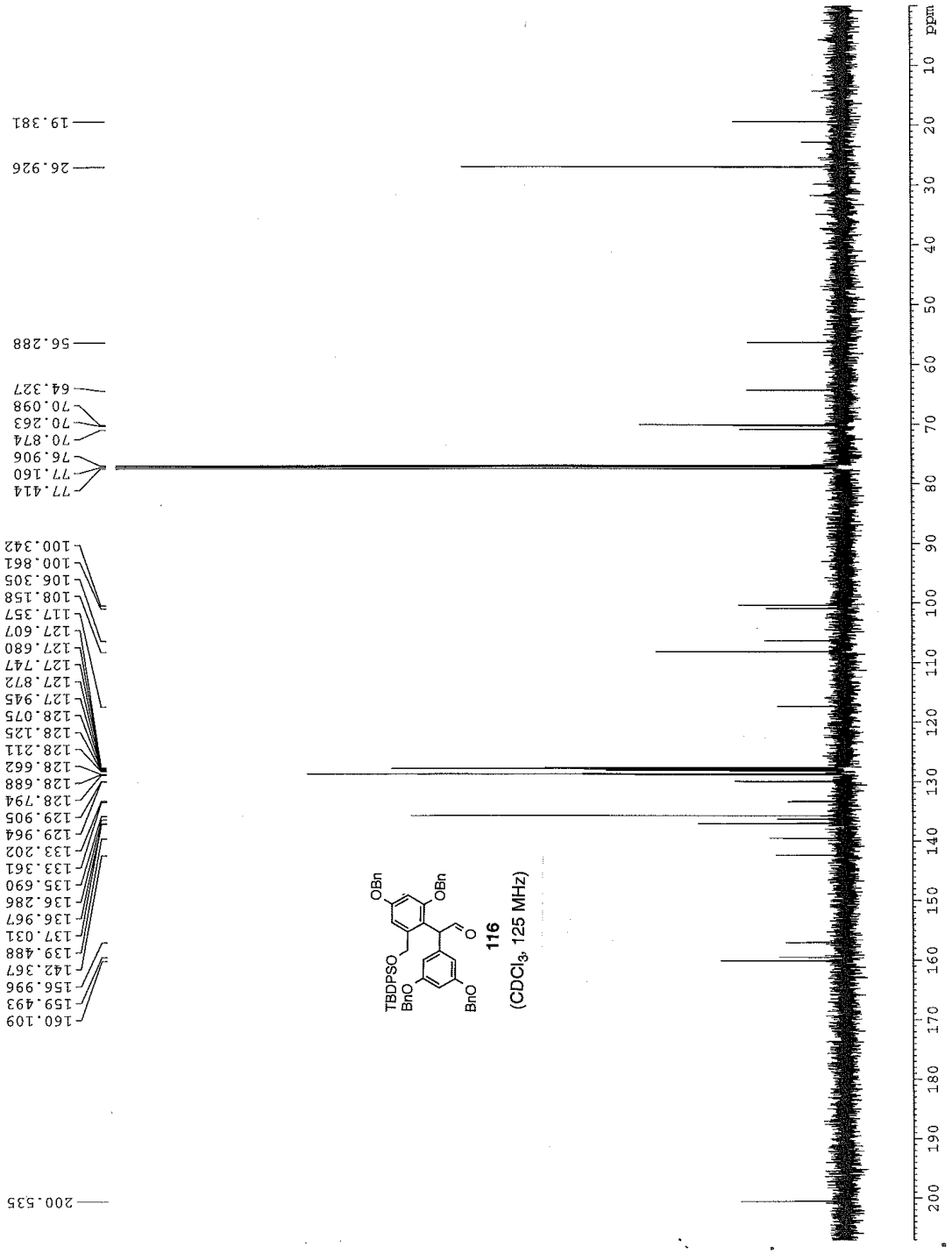

BnO
BnO
Br
OBn
BnO
O
O
114
(CDCl3, 400 MHz)
7.415
7.394
7.377
7.358
7.351
7.345
7.339
7.260
6.830
6.824
6.818
6.744
6.737
6.604
6.597
5.424
5.126
5.076
5.010
23.166
0.990
0.999
1.000
2.003
2.064
4.142
2.007
ppm

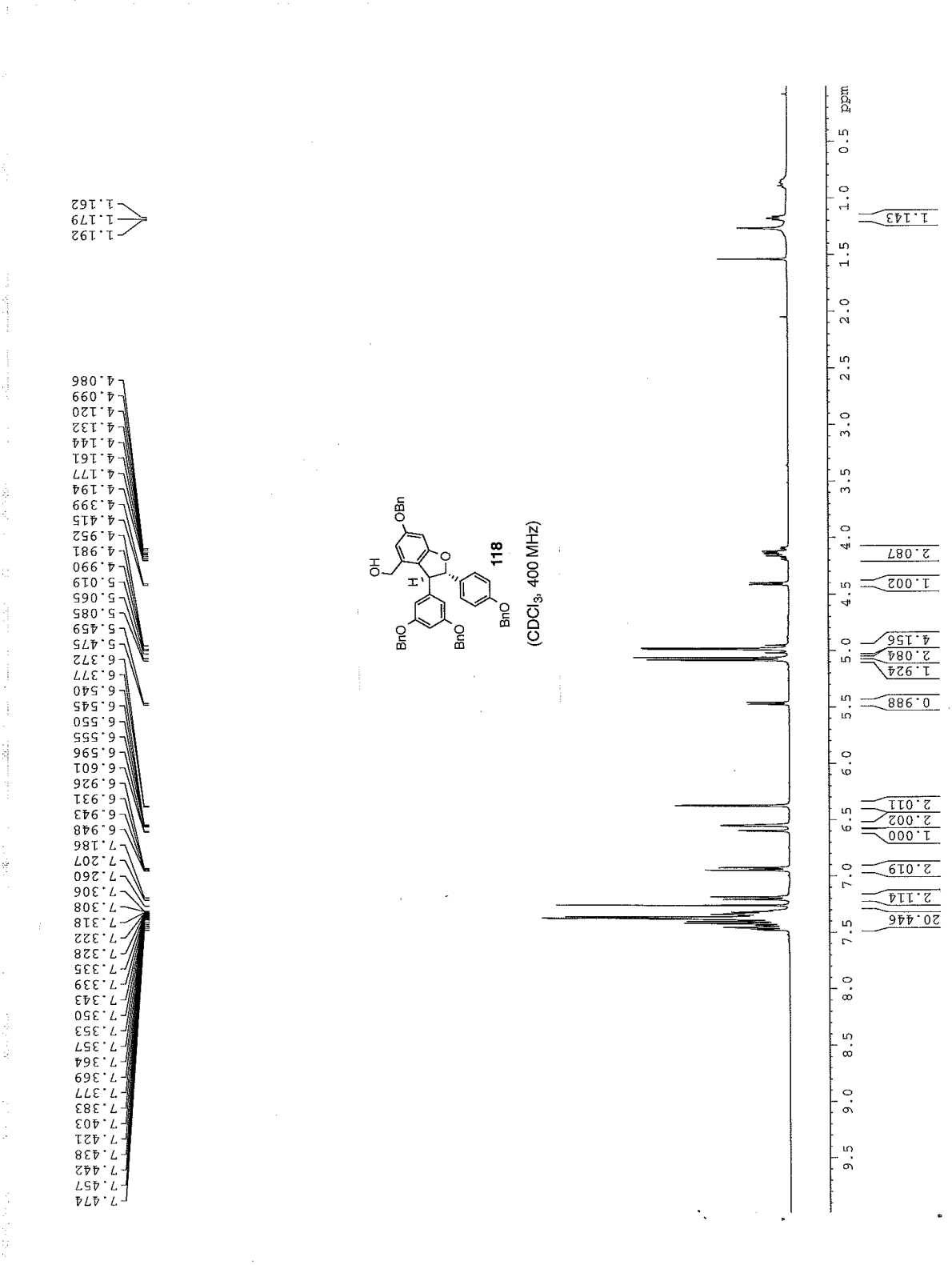

66.719
70.496
70.550
71.158
76.842
77.160
77.478
101.915
104.714
107.485
107.754
108.804
127.164
127.681
127.767
128.149
128.287
128.314
128.764
128.784
128.803
131.981
136.439
136.468
136.569
137.382
156.114
158.941
159.981
165.972
BnO
BnO
Br
OBn
BnO
114
(CDCl3, 100 MHz)
ppm

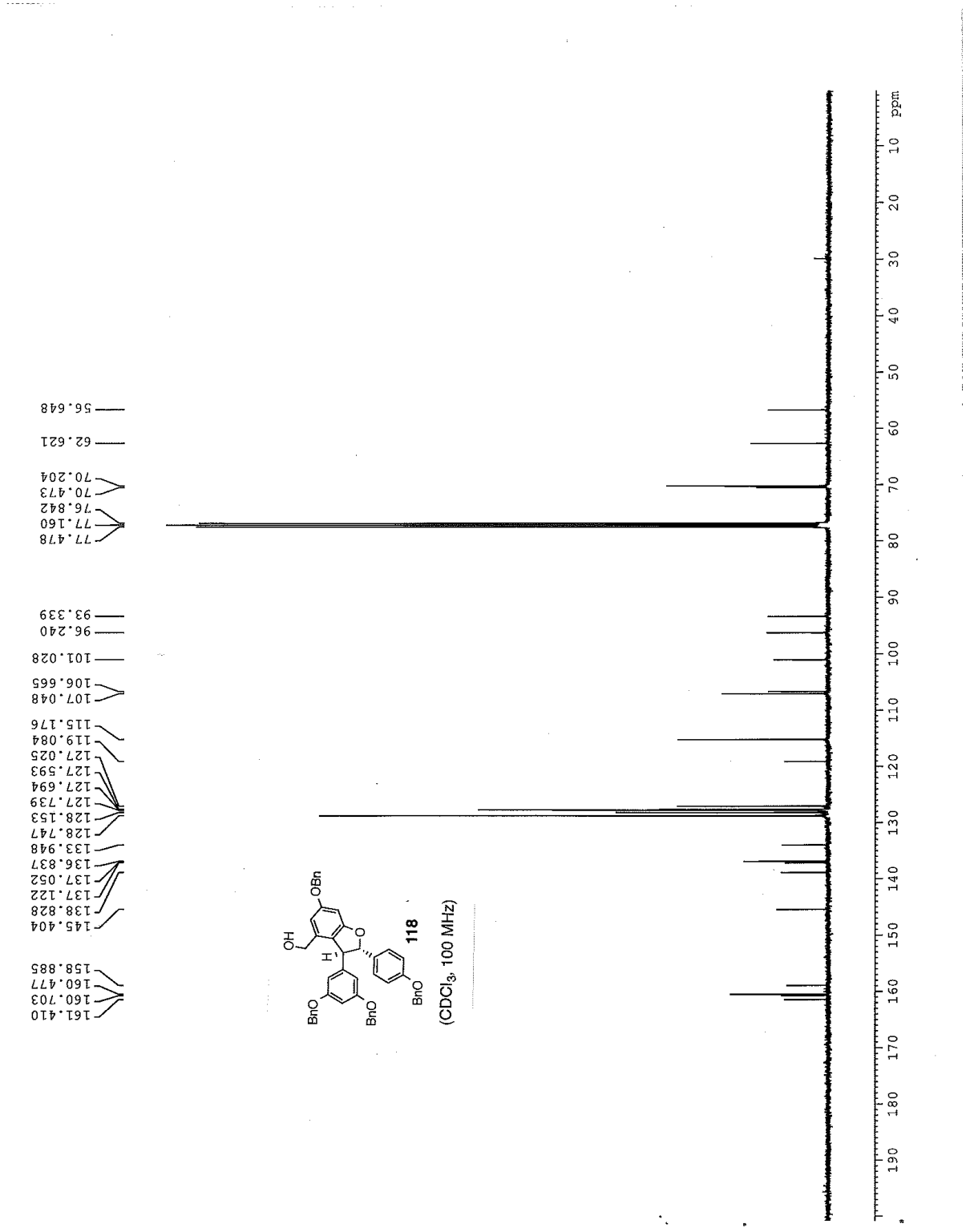

OBn
OBn
TBDPSO
BnO
BnO
O
115
(CDCl3, 400 MHz)
0.995
4.689
4.845
4.980
5.093
6.519
6.525
6.792
6.798
6.803
6.914
6.919
6.932
6.942
6.951
6.955
7.022
7.028
7.182
7.186
7.194
7.199
7.260
7.297
7.301
7.304
7.363
7.372
7.378
7.456
7.461
7.575
7.579
7.595
7.598
9.051
2.070
3.994
2.007
2.006
1.000
1.005
3.014
2.003
3.061
21.485
4.060
ppm

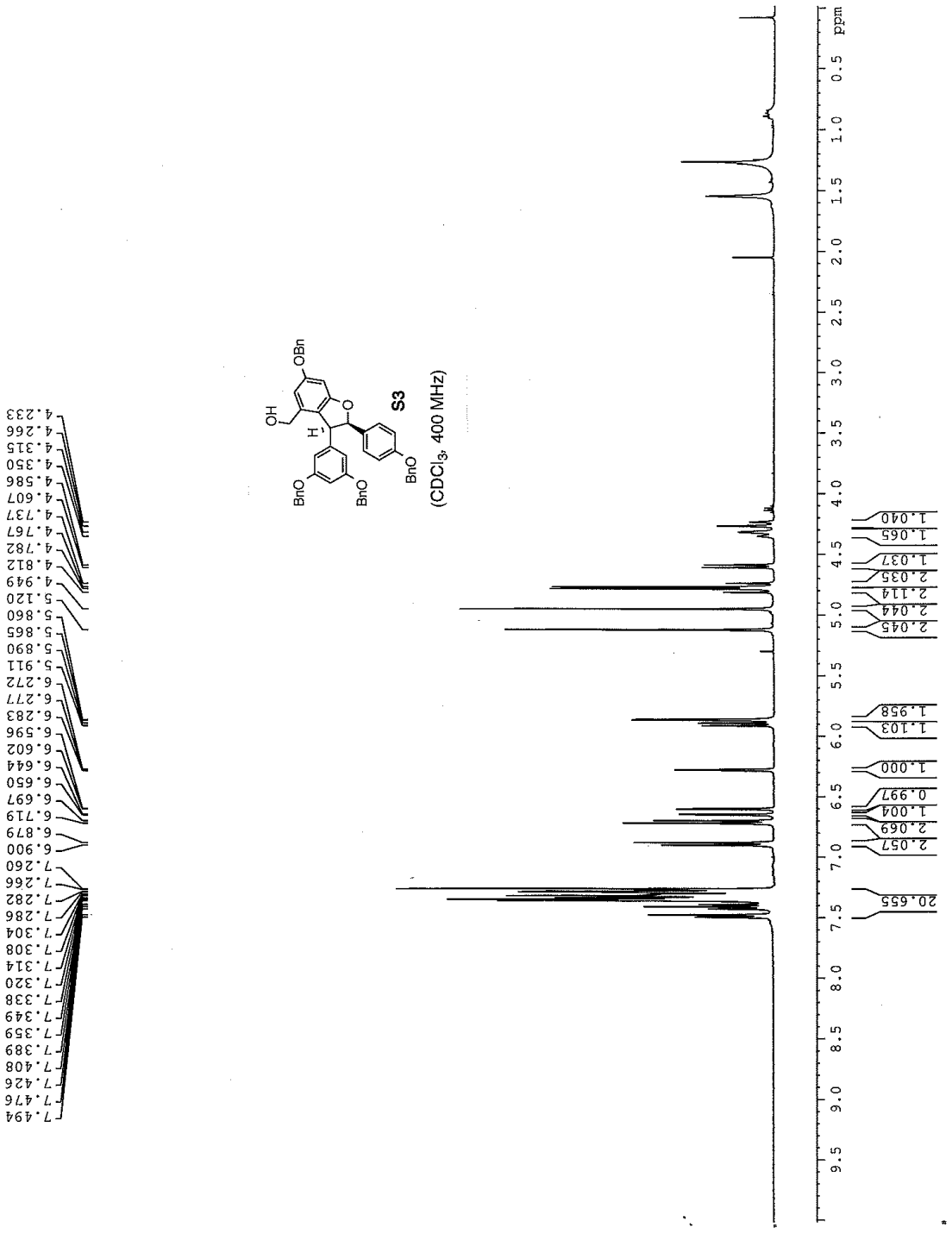

19.359
26.889
63.492
70.264
70.303
70.407
76.841
77.159
77.477
99.736
104.968
107.083
108.239
120.306
126.952
127.680
127.732
127.820
128.200
128.265
128.377
128.751
128.814
129.780
133.365
135.613
136.501
136.736
136.772
141.126
142.329
157.503
160.032
160.901
196.571
OBn
OBn
TBDPSO
BnO
BnO
O
115
(CDCl3, 100 MHz)
ppm

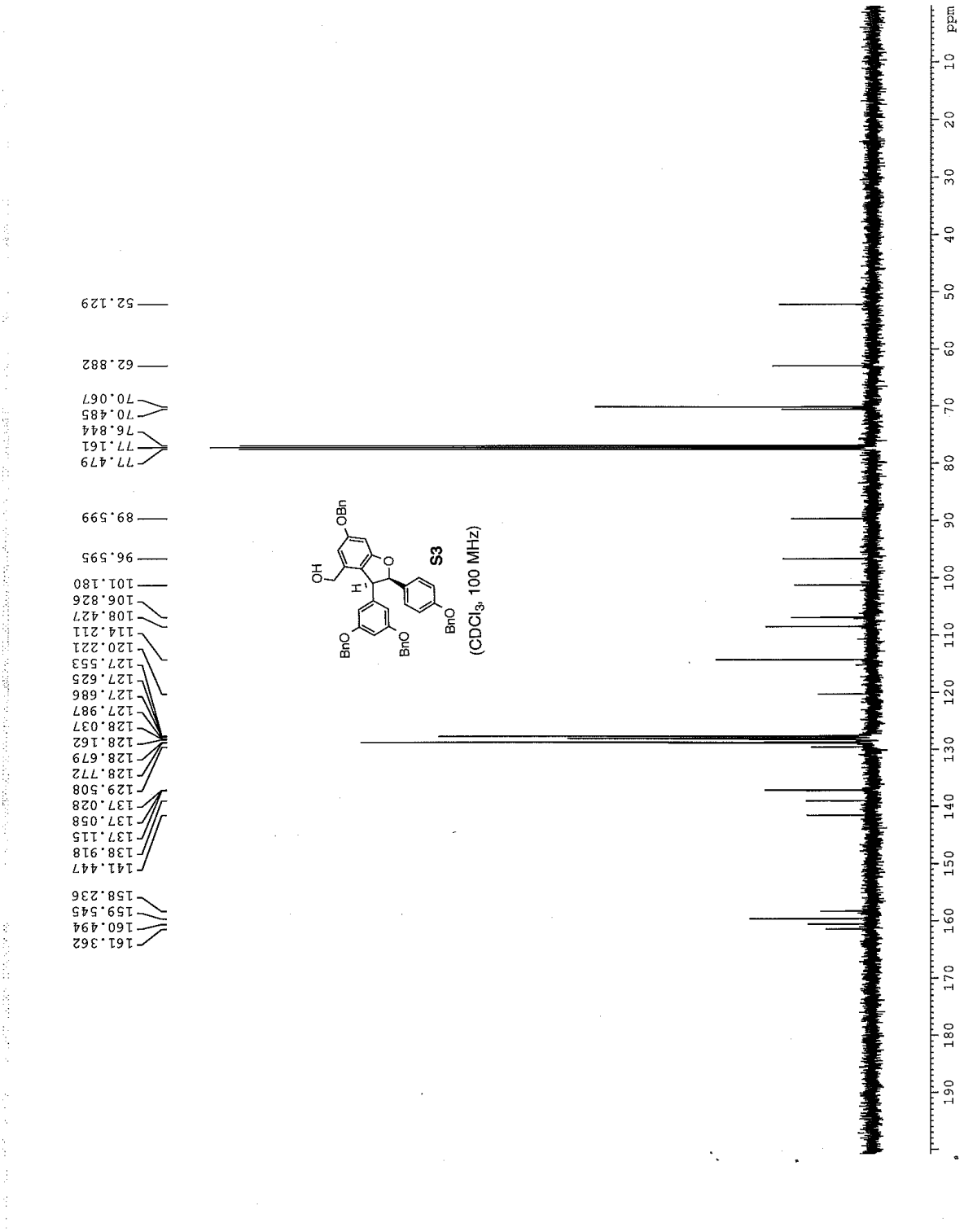

OBn
OBn
TBDPSO
BnO
BnO
O
116
(CDCl3, 500 MHz)
1.038
9.810
7.659
7.656
7.647
7.643
7.640
7.612
7.609
7.600
7.596
7.593
7.440
7.437
7.215
6.796
6.791
6.612
6.607
6.491
6.487
6.482
6.360
6.356
5.028
4.996
4.972
4.957
4.934
4.879
4.856
4.839
4.816
4.760
4.734
4.716
4.594
4.567
ppm
9.325
1.977
2.133
4.233
1.027
1.012
1.011
1.000
1.001
1.046
2.002
27.768
2.054
2.048
0.974

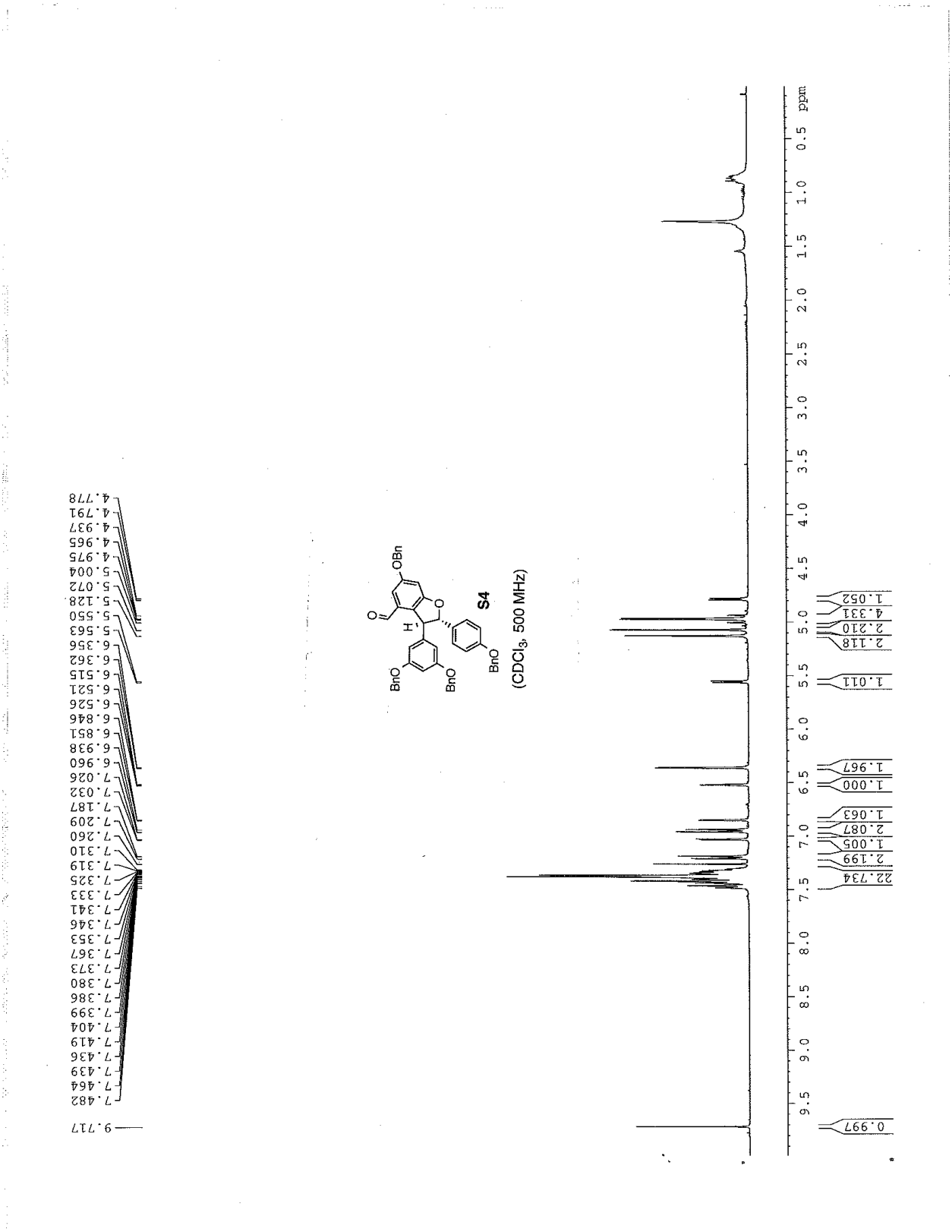

200.535
160.109
159.493
156.996
142.367
139.488
137.031
136.967
136.286
135.690
133.361
133.202
129.964
129.905
128.794
128.688
128.662
128.211
128.125
128.075
127.945
127.872
127.747
127.680
127.607
117.357
108.158
106.305
100.861
100.342
77.414
77.160
76.906
70.874
70.263
70.098
64.327
56.288
26.926
19.381
ppm
OBn
OBn
TBDPSO
BnO
BnO
O
116
(CDCl3, 125 MHz)

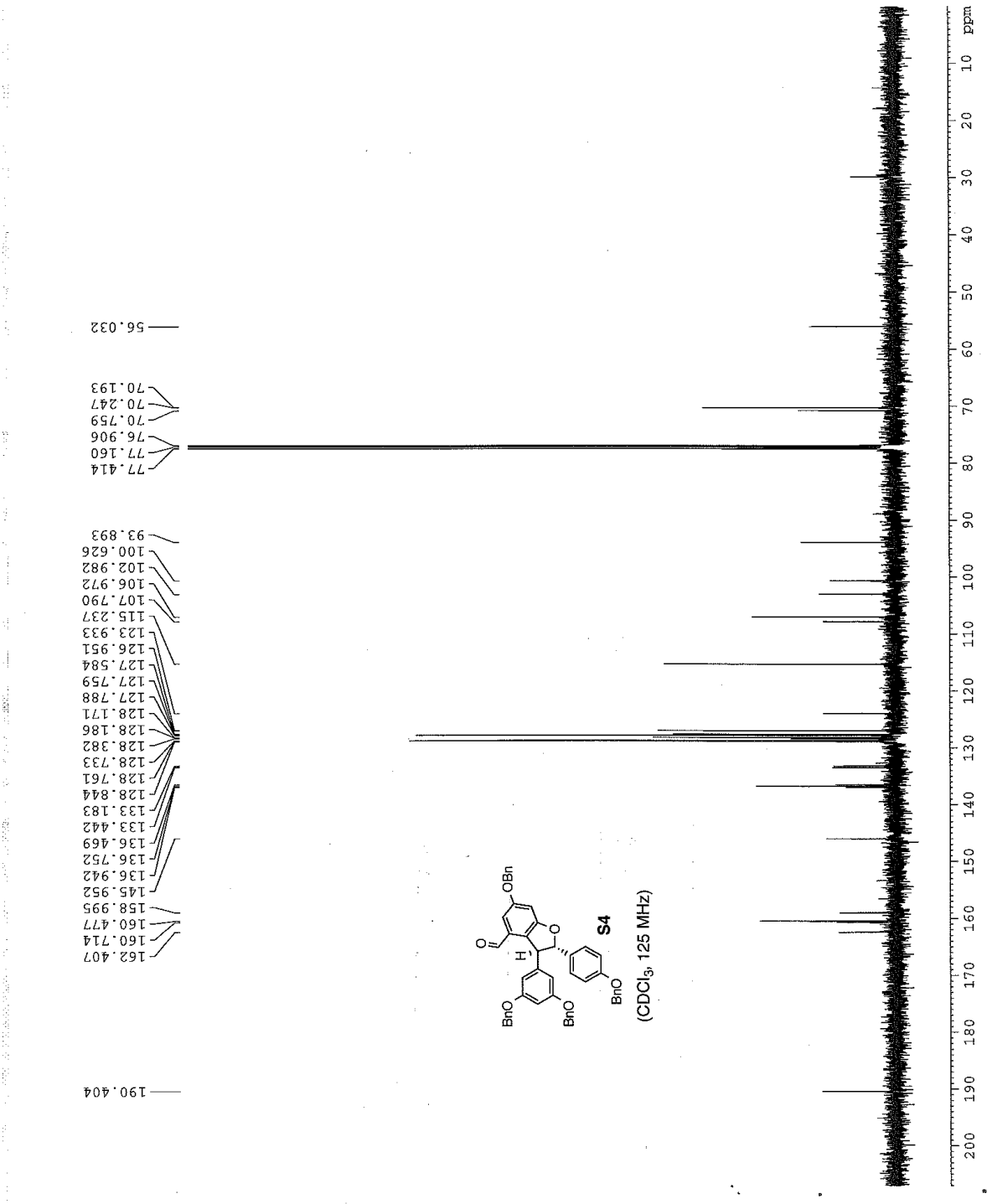

118
(CDCl3, 400 MHz)
OBn
OH
BnO
BnO
BnO
ppm
1.143
2.087
1.002
4.156
2.084
1.924
0.988
2.011
2.002
1.000
2.019
2.114
20.446

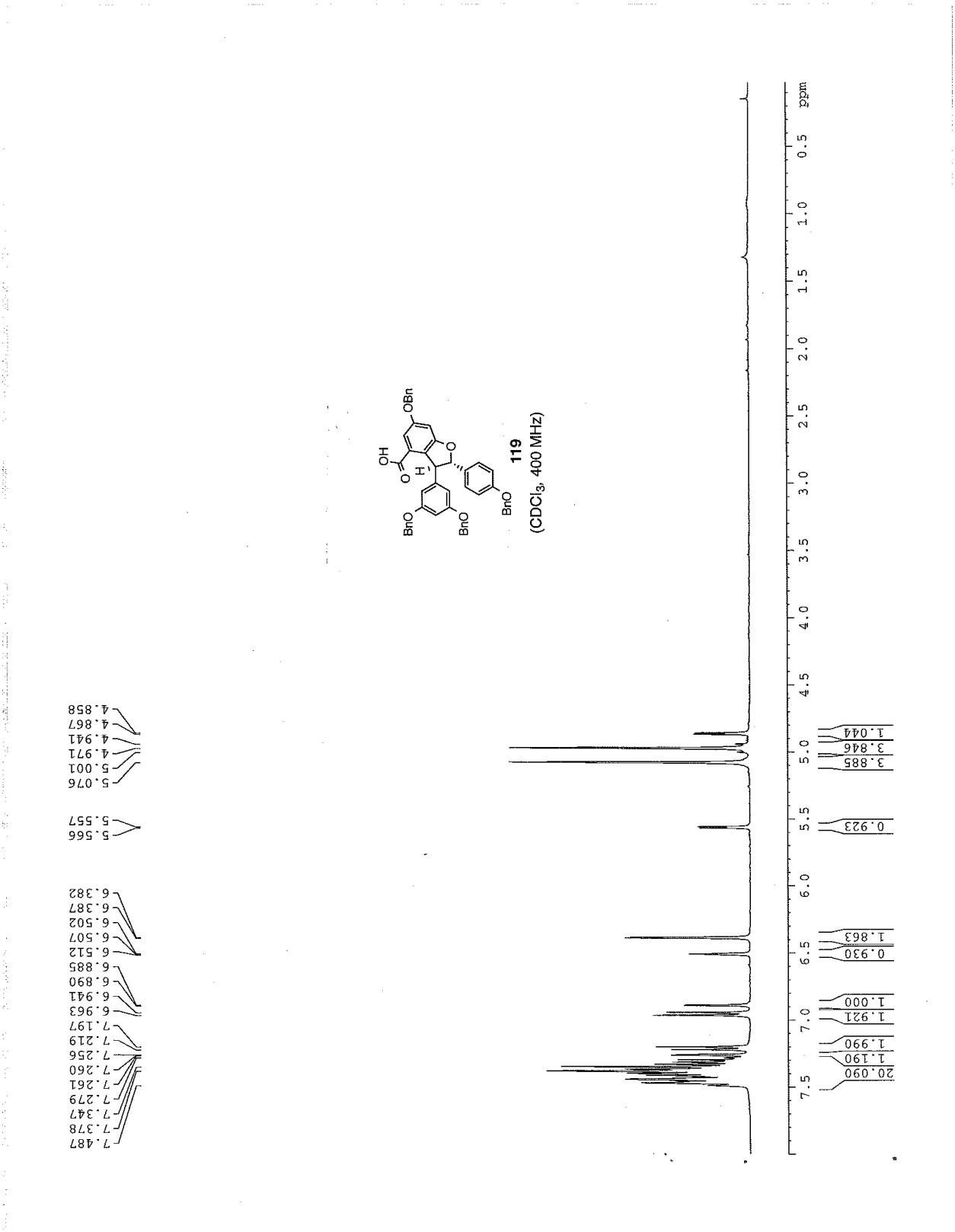

56.648
62.621
70.204
70.473
76.842
77.160
77.478
93.339
96.240
101.028
106.665
107.048
115.176
119.084
127.025
127.593
127.694
127.739
128.153
128.747
133.948
136.837
137.052
137.122
138.828
145.404
158.885
160.477
160.703
161.410
OBn
OH
H
O
BnO
BnO
BnO
118
(CDCl3, 100 MHz)
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

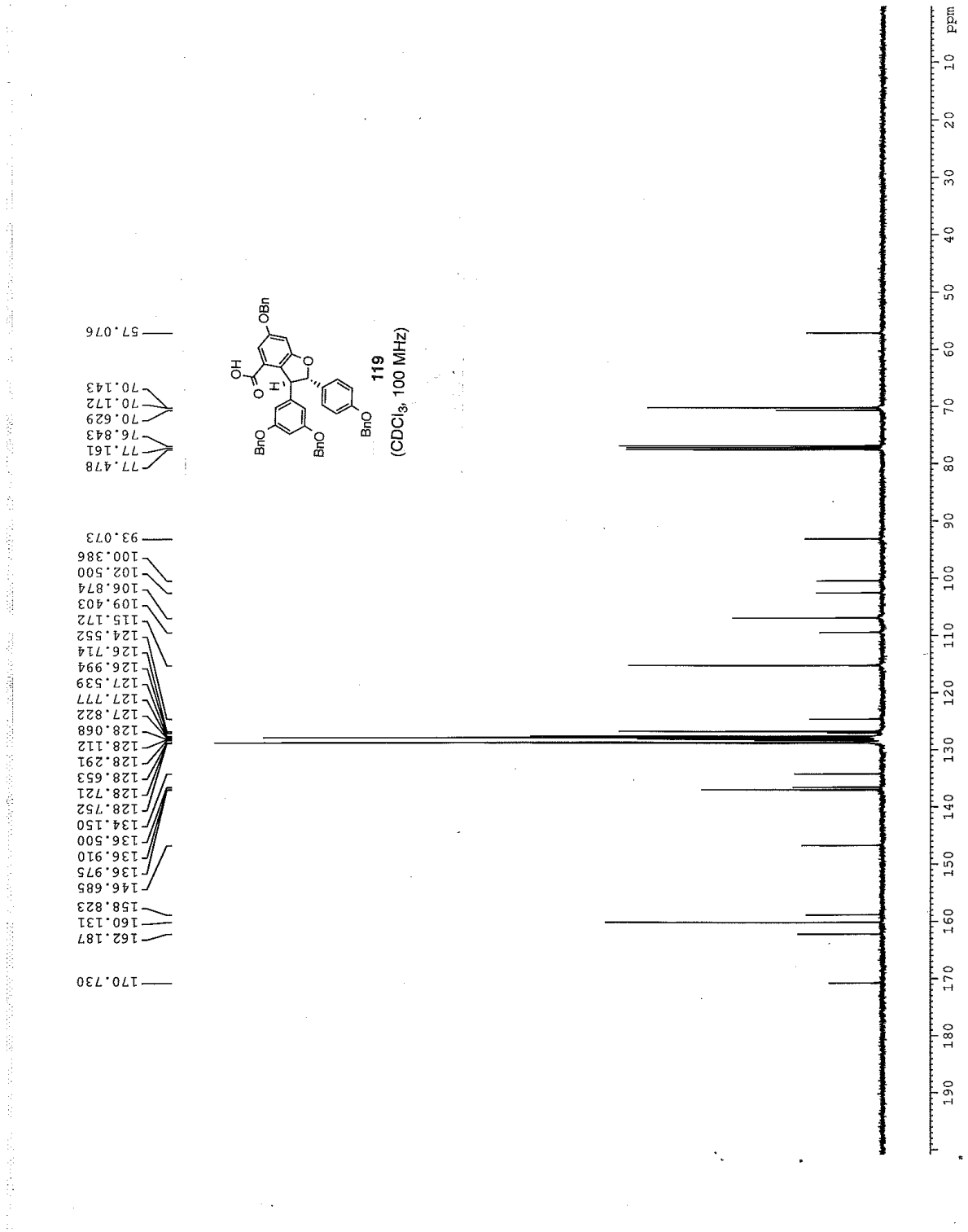

S3
(CDCl3, 400 MHz)
OBn
OH
H
O
BnO
BnO
BnO
4.233
4.266
4.315
4.350
4.586
4.607
4.737
4.767
4.782
4.812
4.949
5.120
5.860
5.865
5.890
5.911
6.272
6.277
6.283
6.596
6.602
6.644
6.650
6.697
6.719
6.879
6.900
7.260
7.266
7.282
7.286
7.304
7.308
7.314
7.320
7.338
7.349
7.359
7.389
7.408
7.426
7.476
7.494
20.655
2.057
2.069
1.004
0.997
1.000
1.103
1.958
2.045
2.044
2.114
2.035
1.037
1.065
1.040
ppm

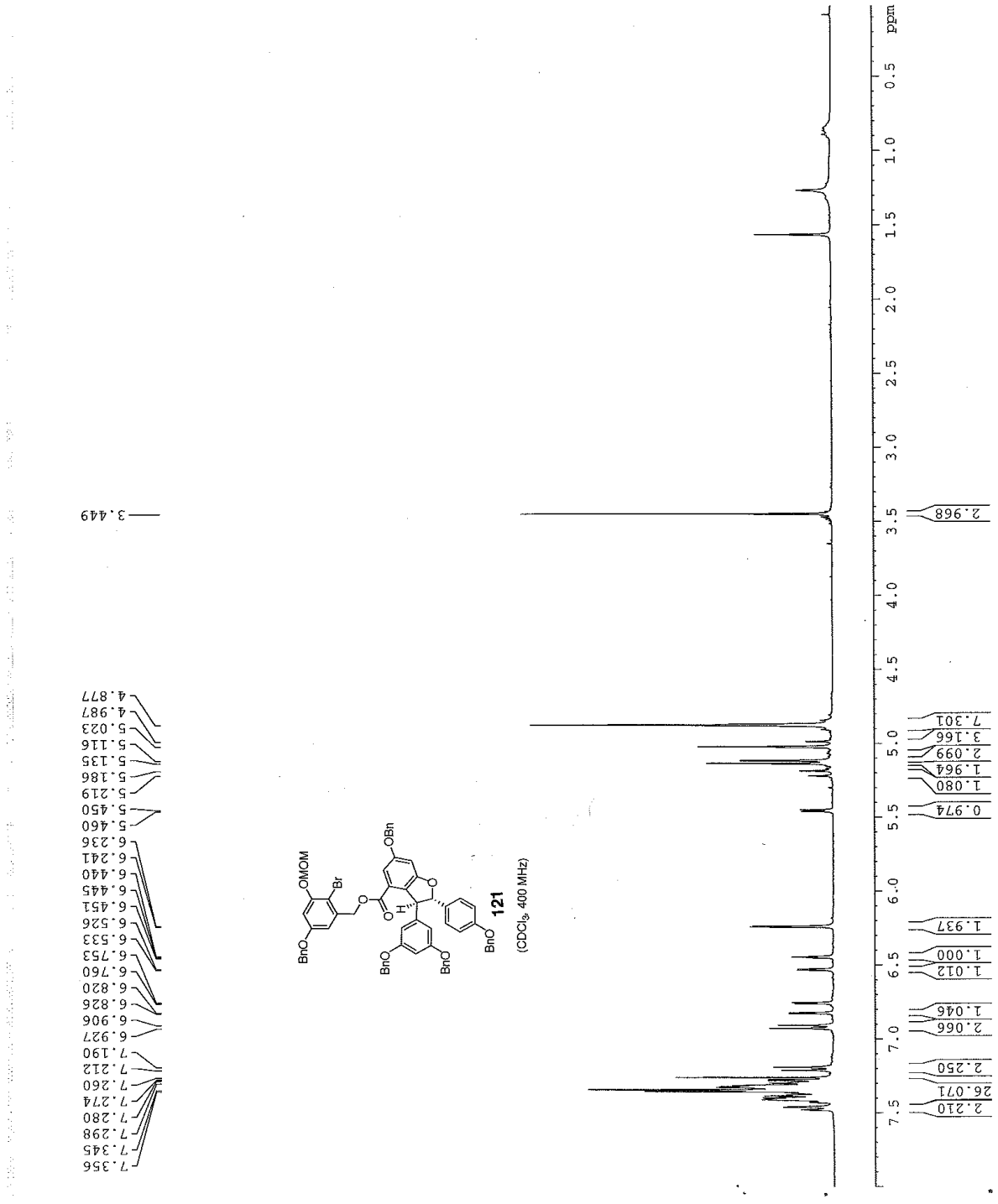

52.129
62.882
70.067
70.485
76.844
77.161
77.479
89.599
96.595
101.180
106.826
108.427
114.211
120.221
127.553
127.625
127.686
127.987
128.037
128.162
128.679
128.772
129.508
137.028
137.058
137.115
138.918
141.447
158.236
159.545
160.494
161.362
OBn
OH
H
O
BnO
BnO
BnO
S3
(CDCl3, 100 MHz)
ppm

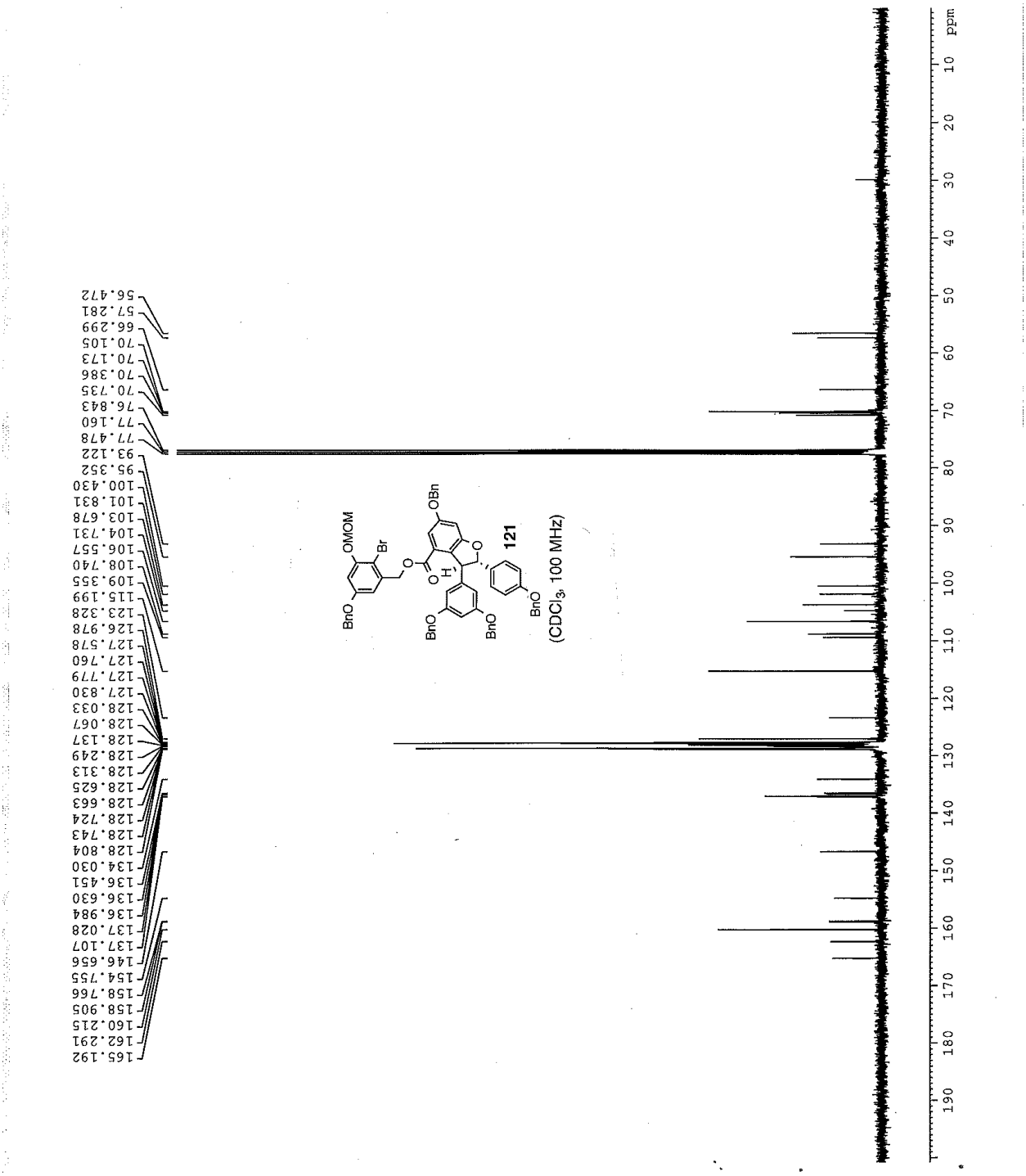

S4
(CDCl3, 500 MHz)
OBn
BnO
BnO
BnO
H1
O
O
9.717
7.482
7.464
7.439
7.436
7.419
7.404
7.399
7.386
7.380
7.373
7.367
7.353
7.346
7.341
7.333
7.325
7.319
7.310
7.260
7.209
7.187
7.032
7.026
6.960
6.938
6.851
6.846
6.526
6.521
6.515
6.362
6.356
5.563
5.550
5.128
5.072
5.004
4.975
4.965
4.937
4.791
4.778
0.997
22.734
2.199
1.005
2.087
1.063
1.000
1.967
1.011
2.118
2.210
4.331
1.052
ppm

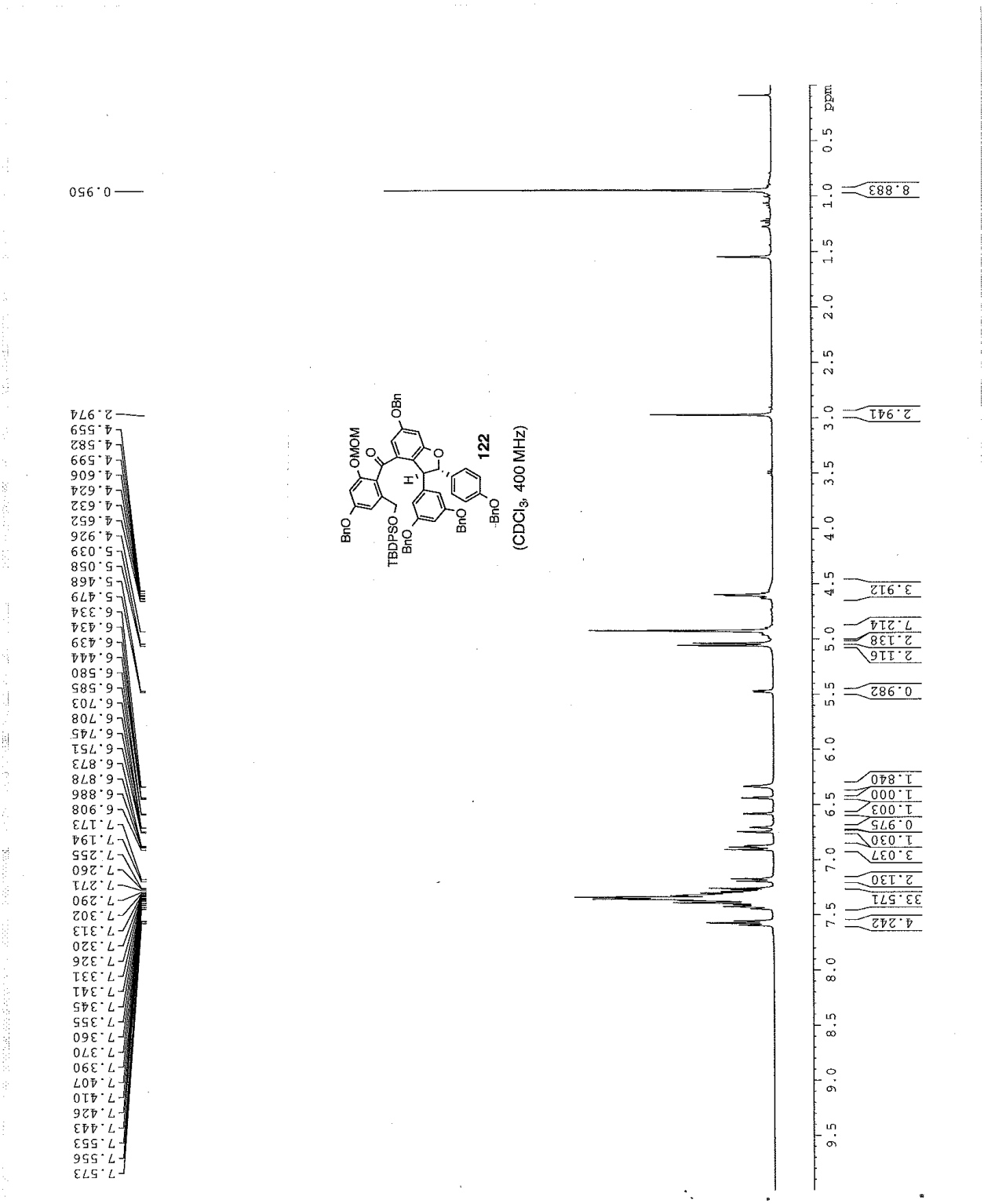

190.404
162.407
160.714
160.477
158.995
145.952
136.942
136.752
136.469
133.442
133.183
128.844
128.761
128.733
128.382
128.186
128.171
127.788
127.759
127.584
126.951
123.933
115.237
107.790
106.972
102.982
100.626
93.893
77.414
77.160
76.906
70.759
70.247
70.193
56.032
OBn
BnO
BnO
BnO
S4
(CDCl3, 125 MHz)
ppm

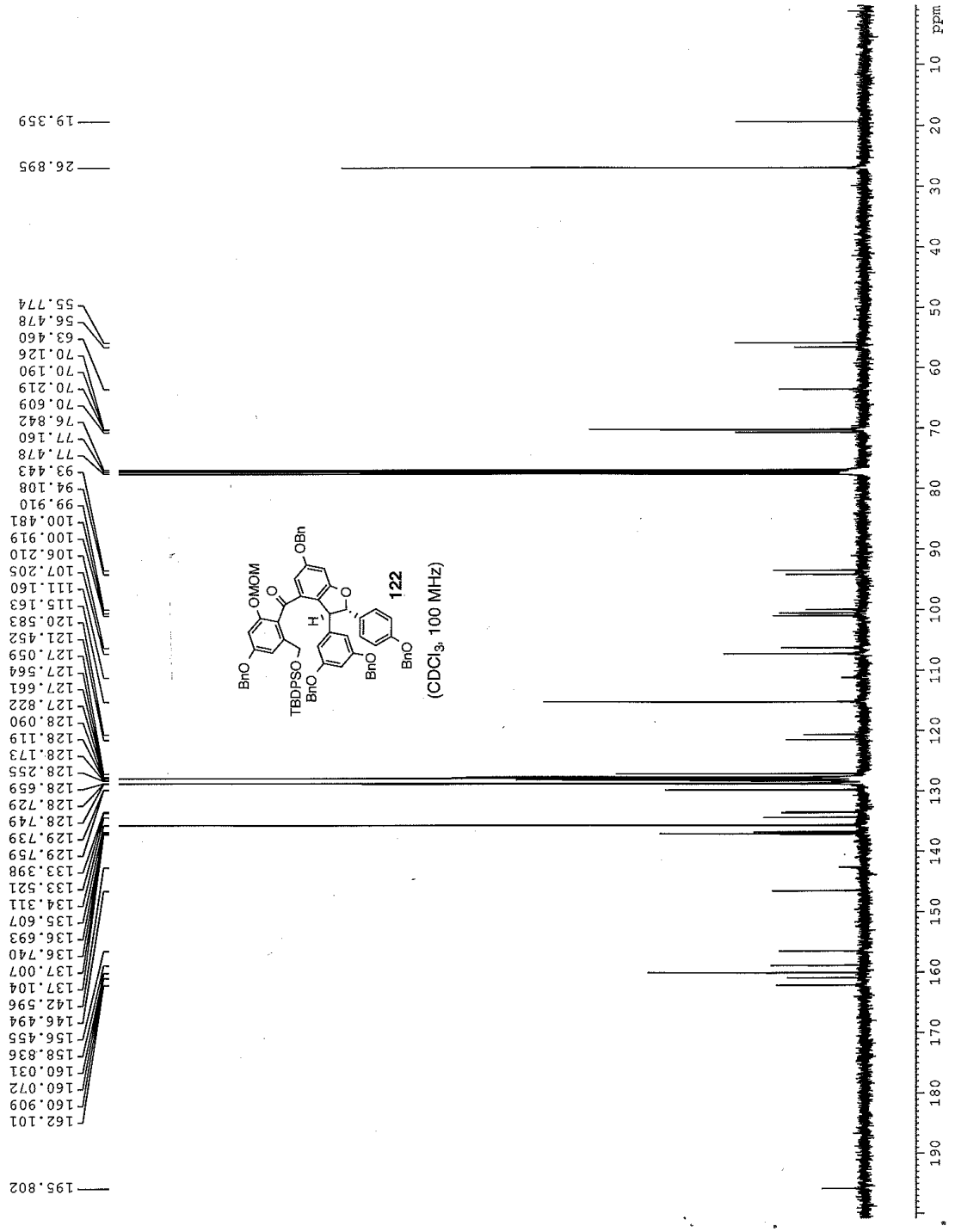

OBn
OH
O
H
BnO
BnO
BnO
119
(CDCl3, 400 MHz)
ppm
20.090
1.190
1.990
1.921
1.000
0.930
1.863
0.923
3.885
3.846
1.044
7.487
7.378
7.347
7.279
7.261
7.260
7.256
7.219
7.197
6.963
6.941
6.890
6.885
6.512
6.507
6.502
6.387
6.382
5.566
5.557
5.076
5.001
4.971
4.941
4.867
4.858

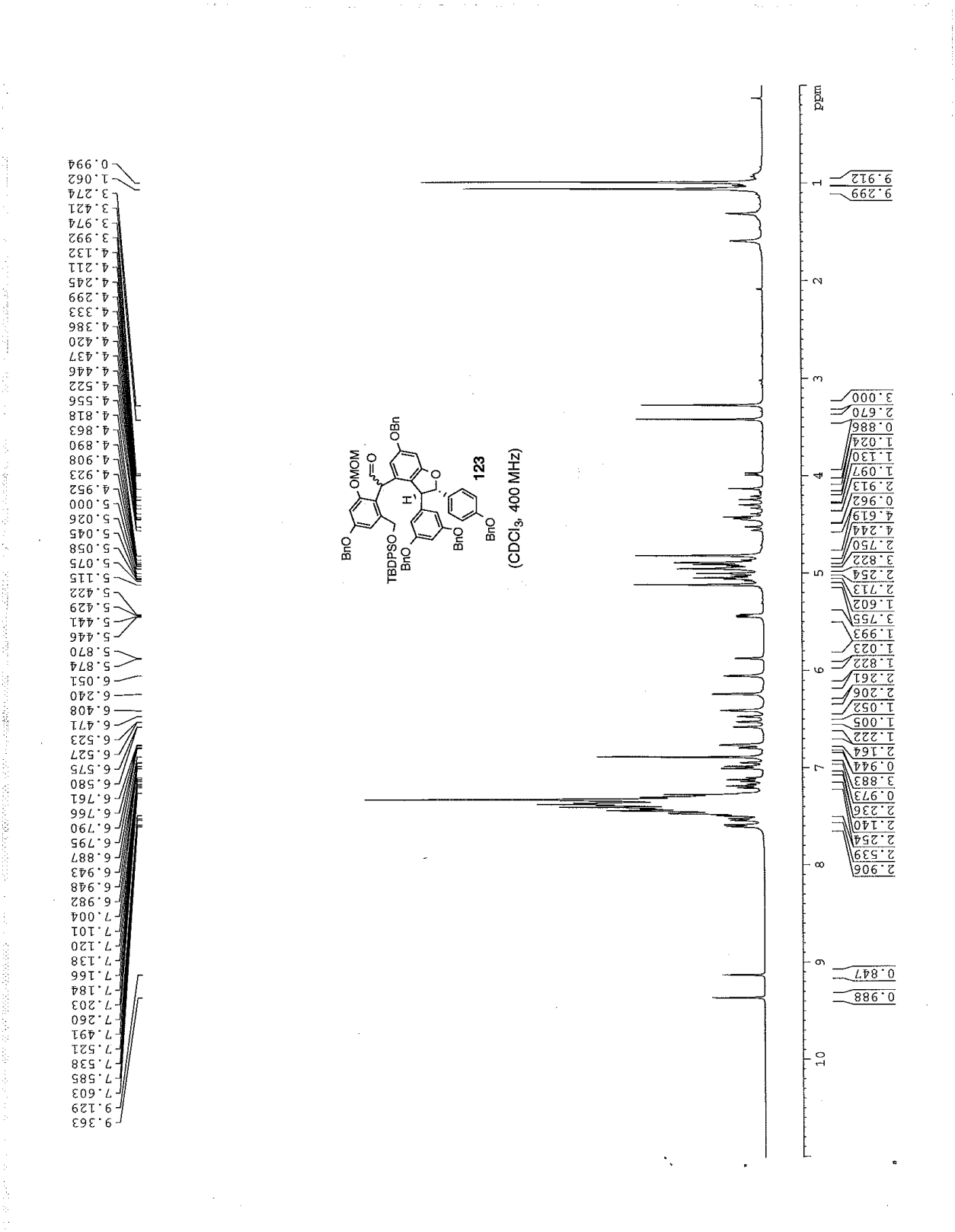

119
(CDCl3, 100 MHz)
OBn
OH
O
H
BnO
BnO
BnO
57.076
70.143
70.172
70.629
76.843
77.161
77.478
93.073
100.386
102.500
106.874
109.403
115.172
124.552
126.714
126.994
127.539
127.777
127.822
128.068
128.112
128.291
128.653
128.721
128.752
134.150
136.500
136.910
136.975
146.685
158.823
160.131
162.187
170.730
ppm

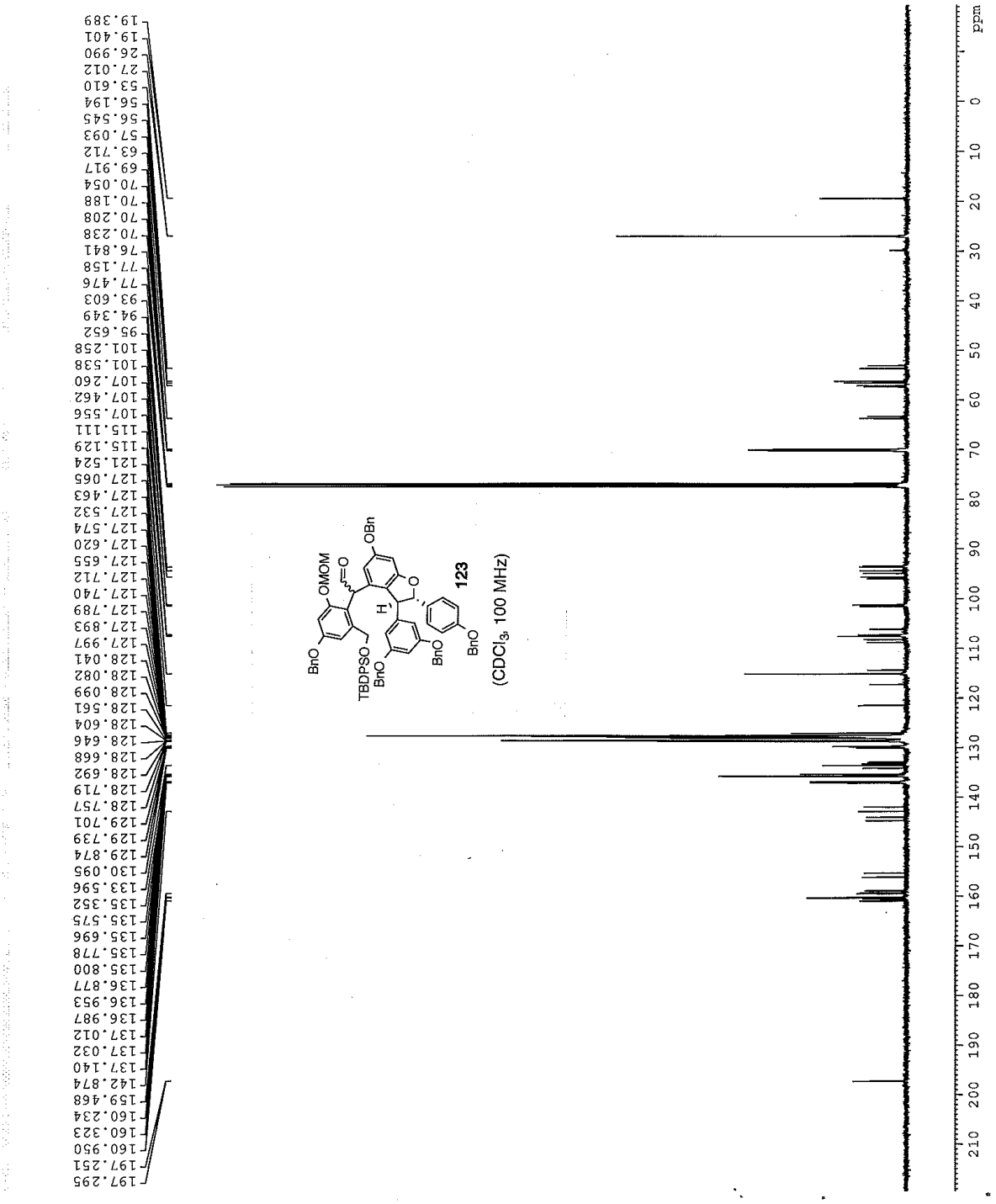

121
(CDCl3, 400 MHz)
ppm

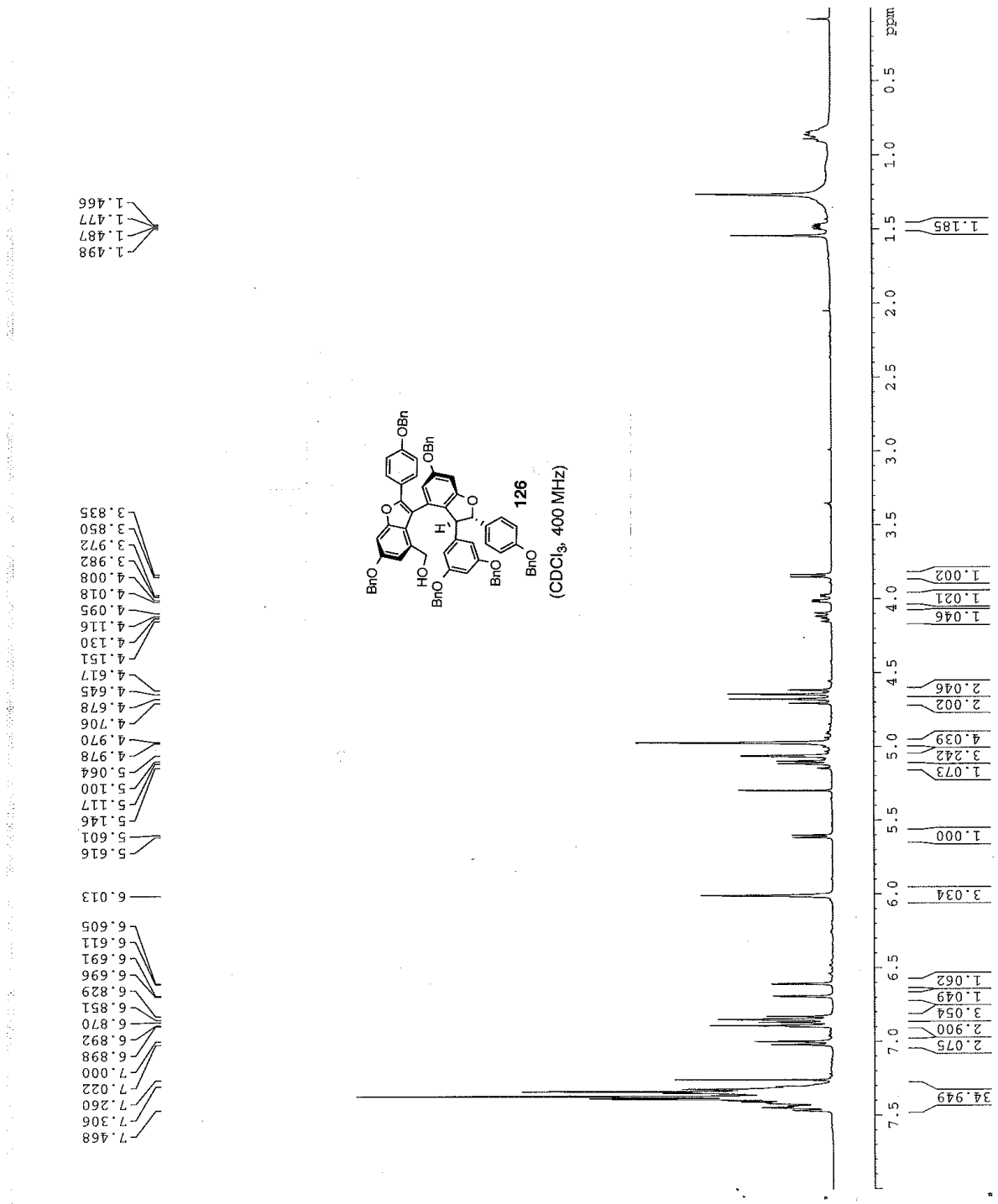

OMOM
Br
OBn
BnO
BnO
BnO
BnO
121
(CDCl3, 100 MHz)
ppm
56.472
57.281
66.299
70.105
70.173
70.386
70.735
76.843
77.160
77.478
93.122
95.352
100.430
101.831
103.678
104.731
106.557
108.740
109.355
115.199
123.328
126.978
127.578
127.760
127.779
127.830
128.033
128.067
128.137
128.249
128.313
128.625
128.663
128.724
128.743
128.804
134.030
136.451
136.630
136.984
137.028
137.107
146.656
154.755
158.766
158.905
160.215
162.291
165.192

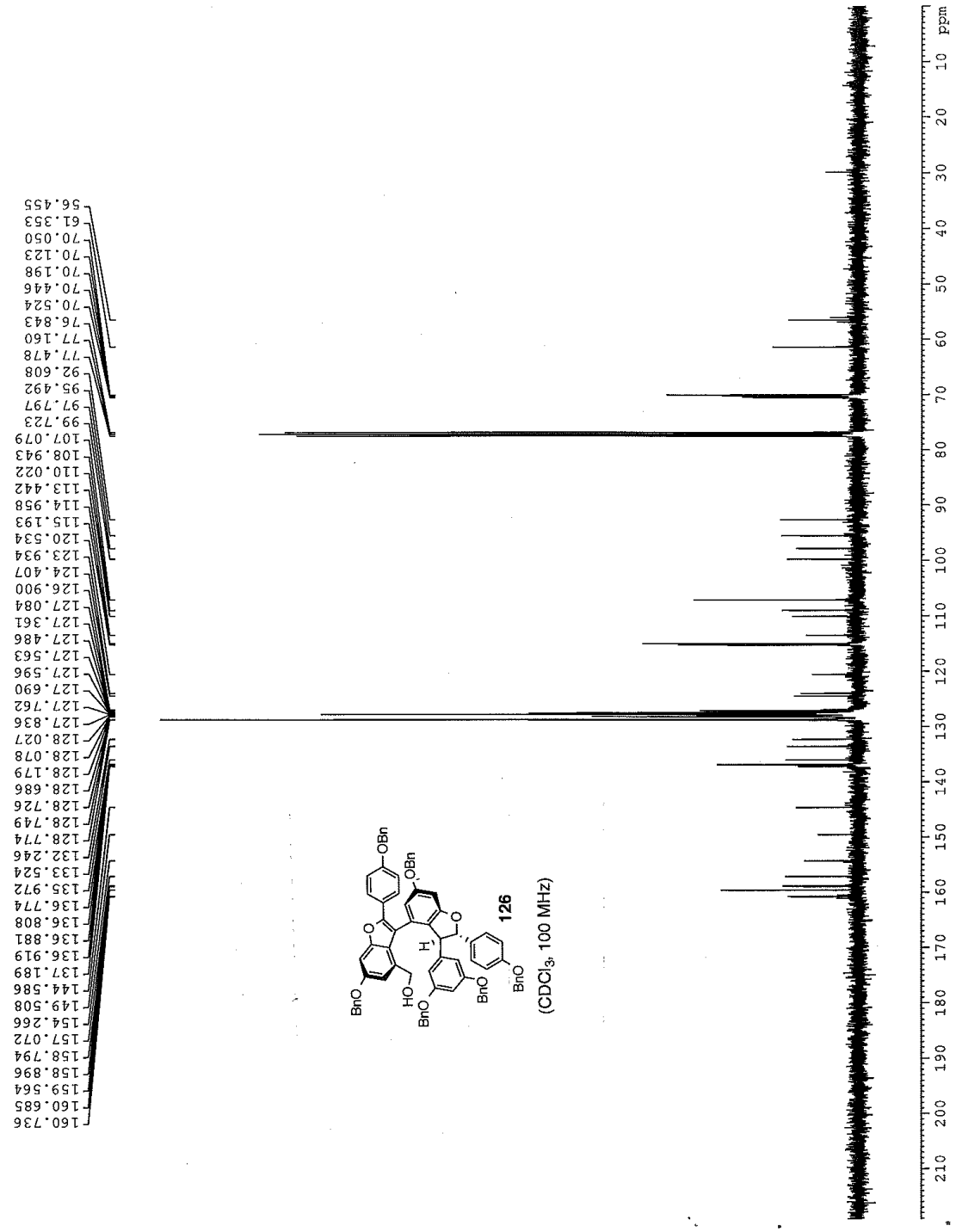

122
(CDCl3, 400 MHz)
OMOM
OBn
TBDPSO
BnO
H
ppm
8.883
2.941
3.912
7.214
2.138
2.116
0.982
1.840
1.000
1.003
0.975
1.030
3.037
2.130
33.571
4.242
0.950
2.974

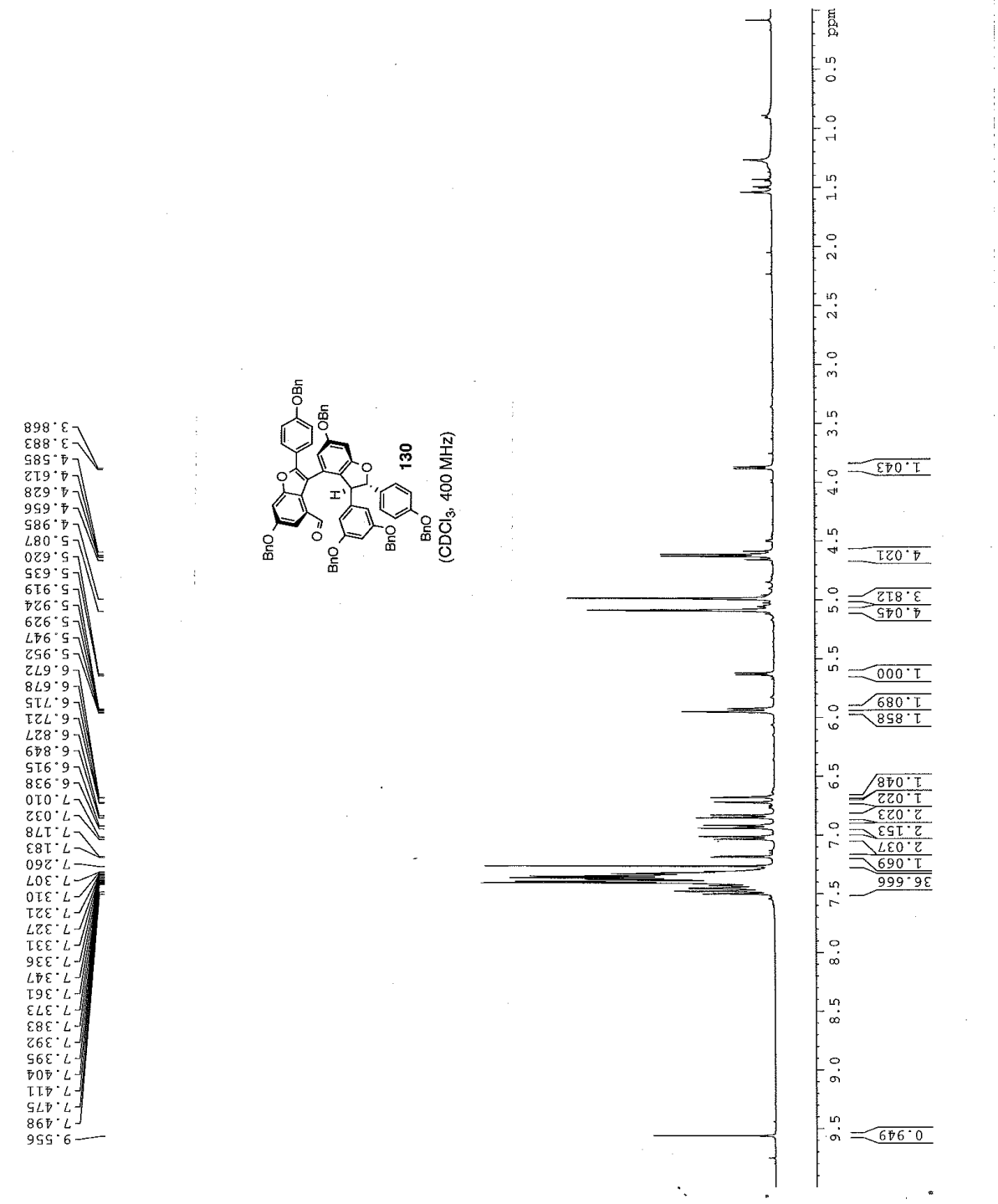

19.359
26.895
55.774
56.478
63.460
70.126
70.190
70.219
70.609
76.842
77.160
77.478
93.443
94.108
99.910
100.481
100.919
106.210
107.205
111.160
115.163
120.583
121.452
127.059
127.564
127.661
127.822
128.090
128.119
128.173
128.255
128.659
128.729
128.749
129.739
129.759
133.398
133.521
134.311
135.607
136.693
136.740
137.007
137.104
142.596
146.494
156.455
158.836
160.031
160.072
160.909
162.101
195.802
OMOM
OBn
BnO
TBDPSO
BnO
BnO
BnO
H
O
O
122
(CDCl3, 100 MHz)
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

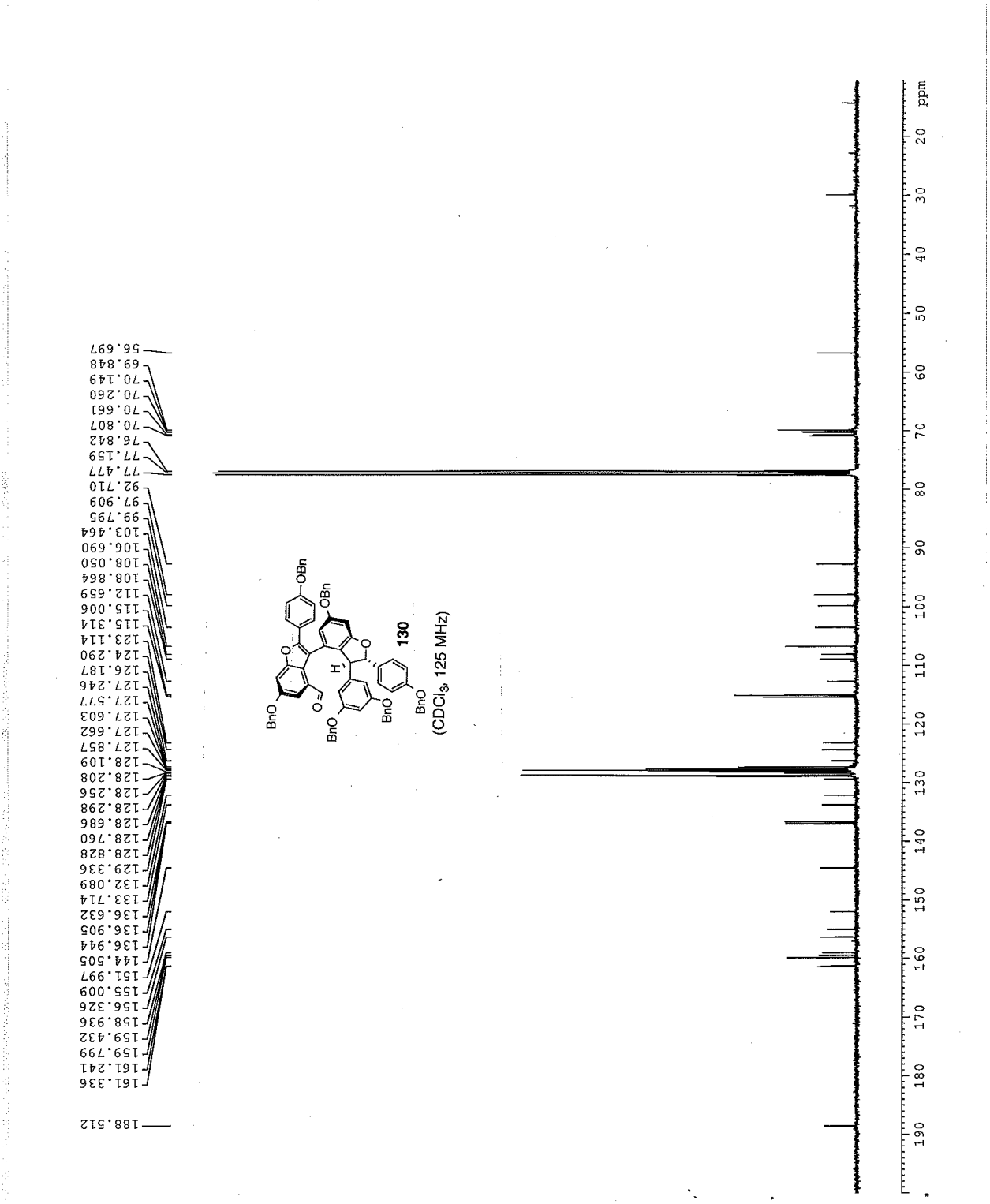

OMOM
OBn
TBDPSO
BnO
BnO
BnO
BnO
H
123
(CDCl3, 400 MHz)
ppm

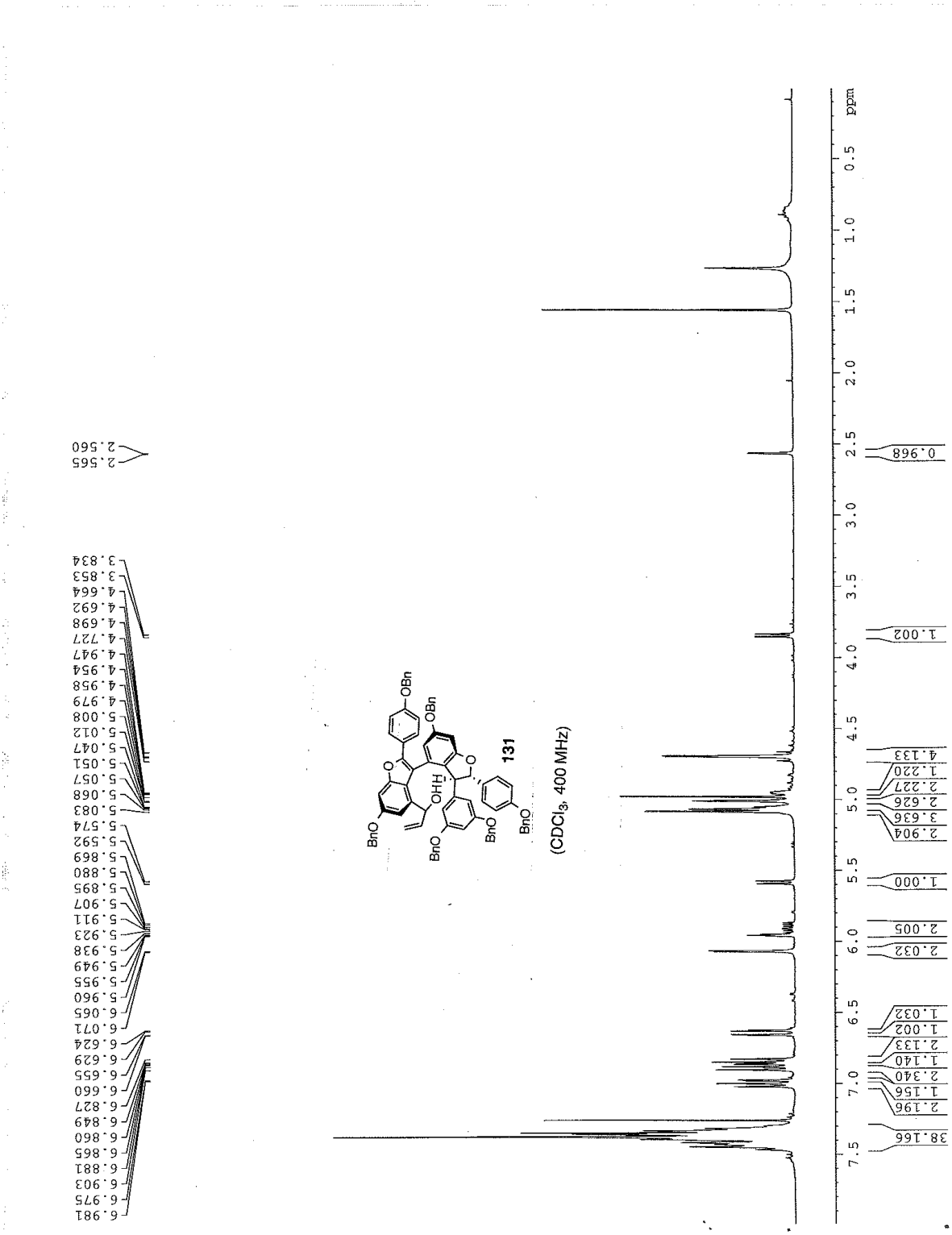

OMOM
OBn
TBDPSO
BnO
BnO
BnO
BnO
H
O
123
(CDCl3, 100 MHz)
ppm

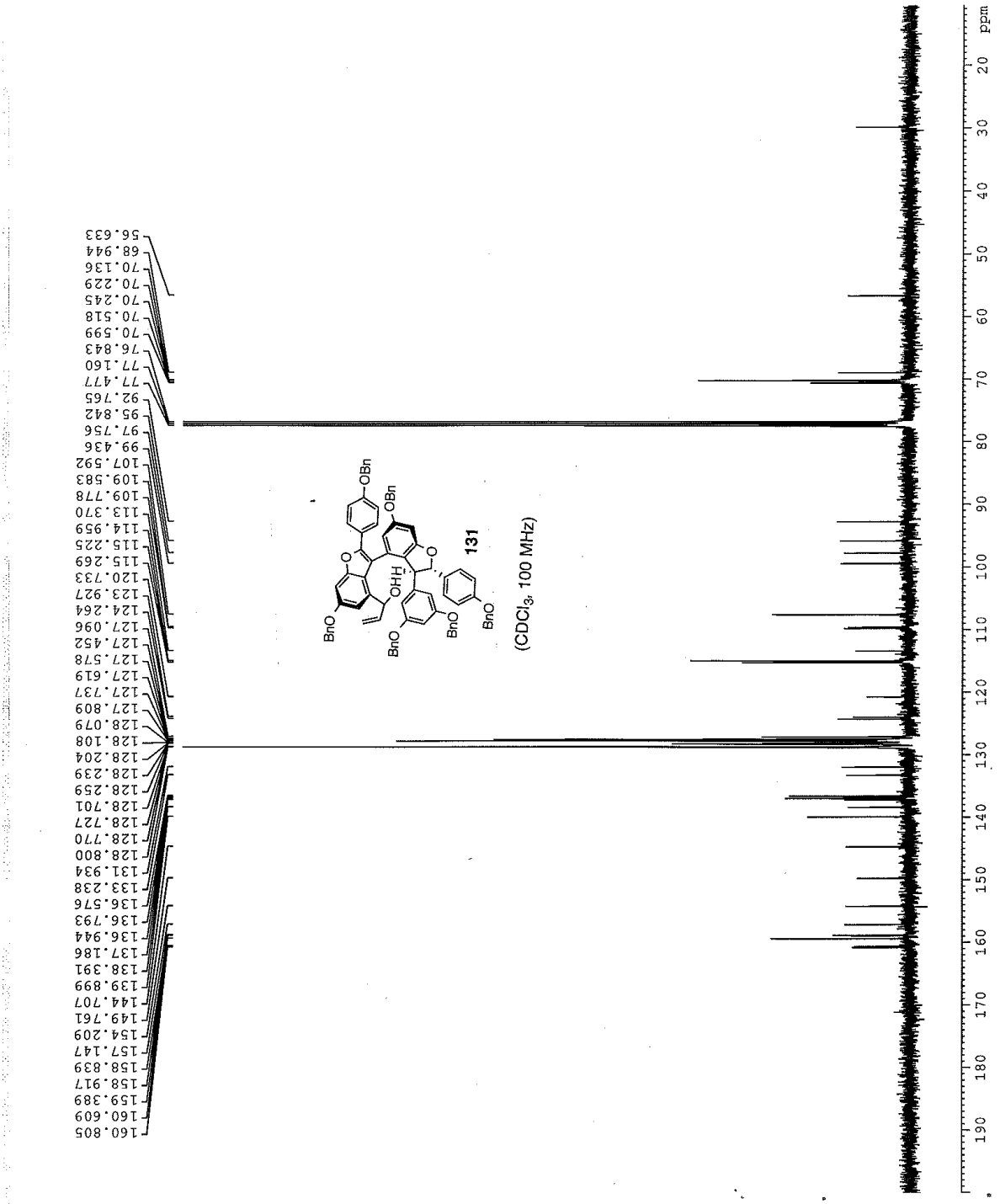

126
(CDCl3, 400 MHz)
OBn
OBn
BnO
BnO
BnO
BnO
HO
H
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
34.949
2.075
2.900
3.054
1.049
1.062
3.034
1.000
1.073
3.242
4.039
2.002
2.046
1.046
1.021
1.002
1.185
7.468
7.306
7.260
7.022
7.000
6.898
6.892
6.870
6.851
6.829
6.696
6.691
6.611
6.605
6.013
5.616
5.601
5.146
5.117
5.100
5.064
4.978
4.970
4.706
4.678
4.645
4.617
4.151
4.130
4.116
4.095
4.018
4.008
3.982
3.972
3.850
3.835
1.498
1.487
1.477
1.466

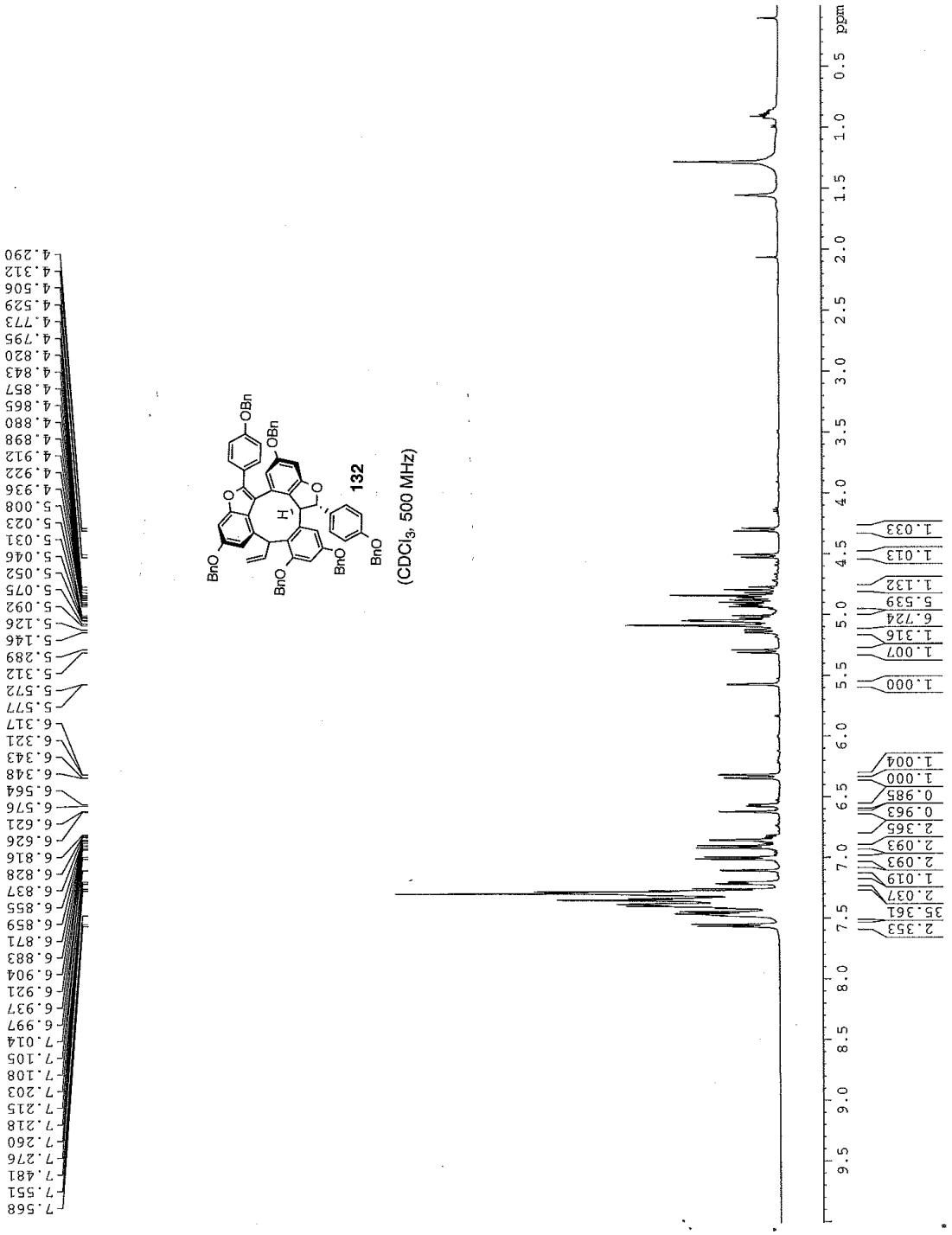

126
(CDCl3, 100 MHz)
ppm

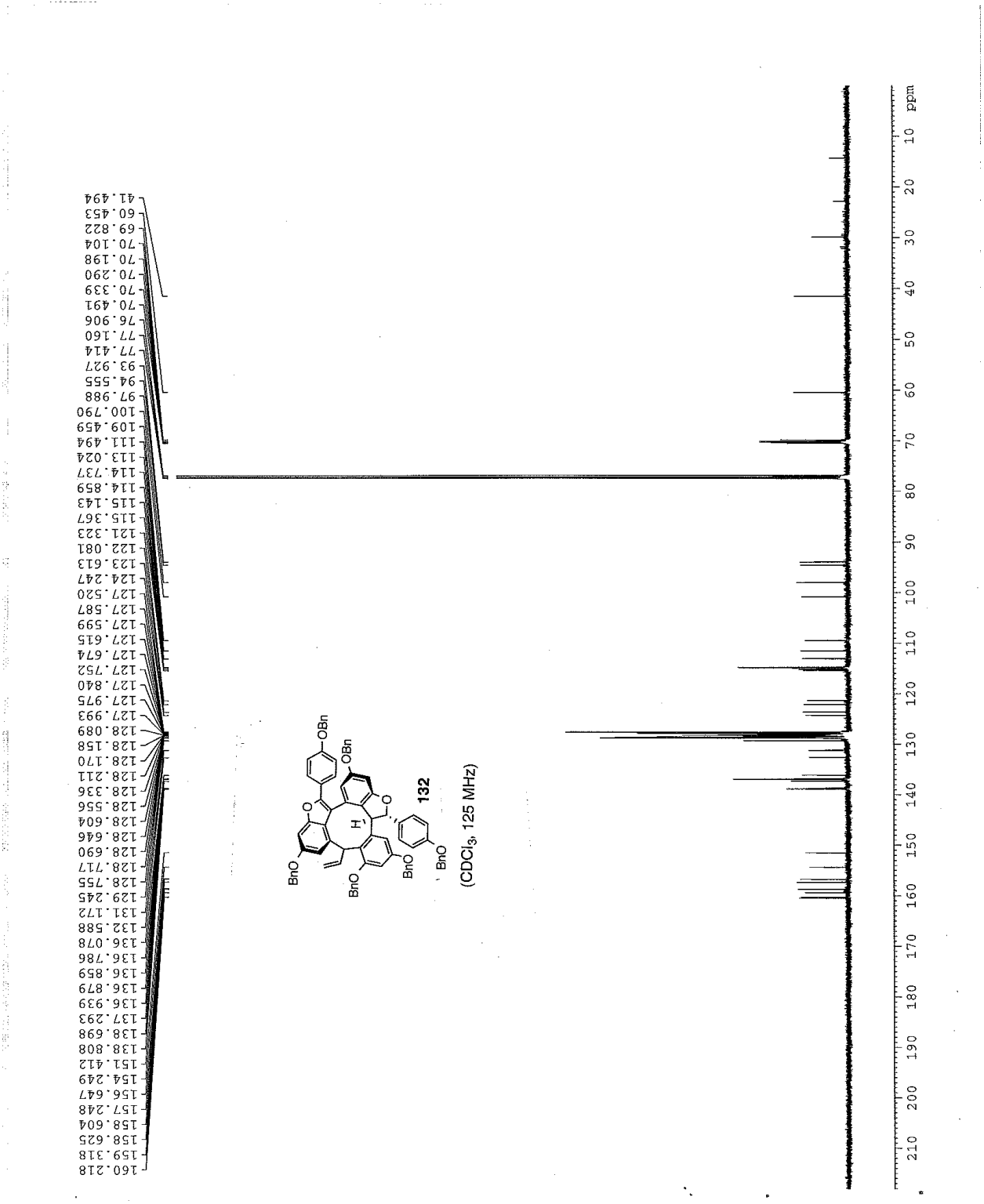

130
(CDCl3, 400 MHz)
ppm

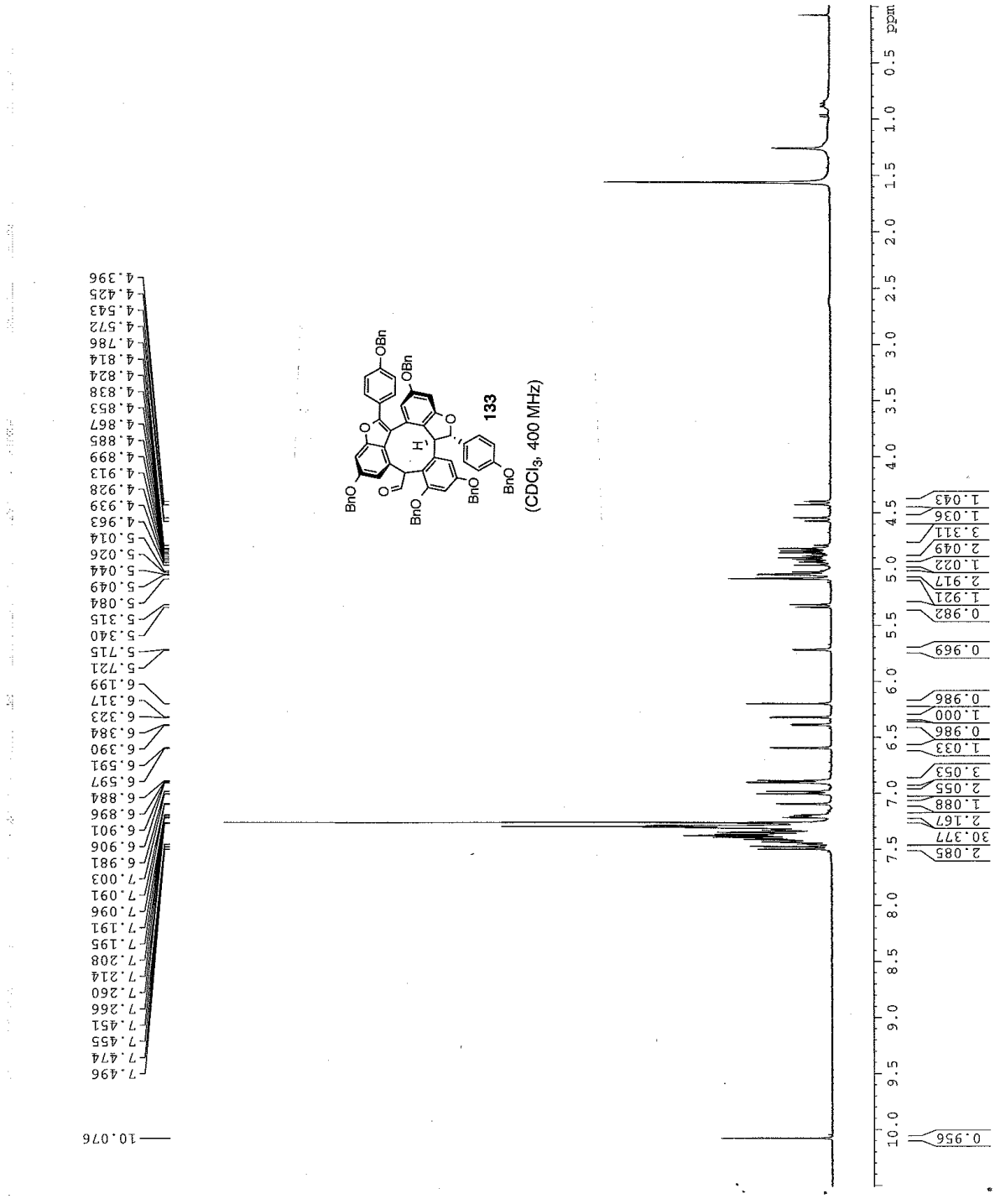

188.512
161.336
161.241
159.799
159.432
158.936
156.326
155.009
151.997
144.505
136.944
136.905
136.632
133.714
132.089
129.336
128.828
128.760
128.686
128.298
128.256
128.208
128.109
127.857
127.662
127.603
127.577
127.246
126.187
124.290
123.114
115.314
115.006
112.659
108.864
108.050
106.690
103.464
99.795
97.909
92.710
77.477
77.159
76.842
70.807
70.661
70.260
70.149
69.848
56.697
OBn
OBn
BnO
BnO
BnO
BnO
O
O
H
O
130
(CDCl3, 125 MHz)
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

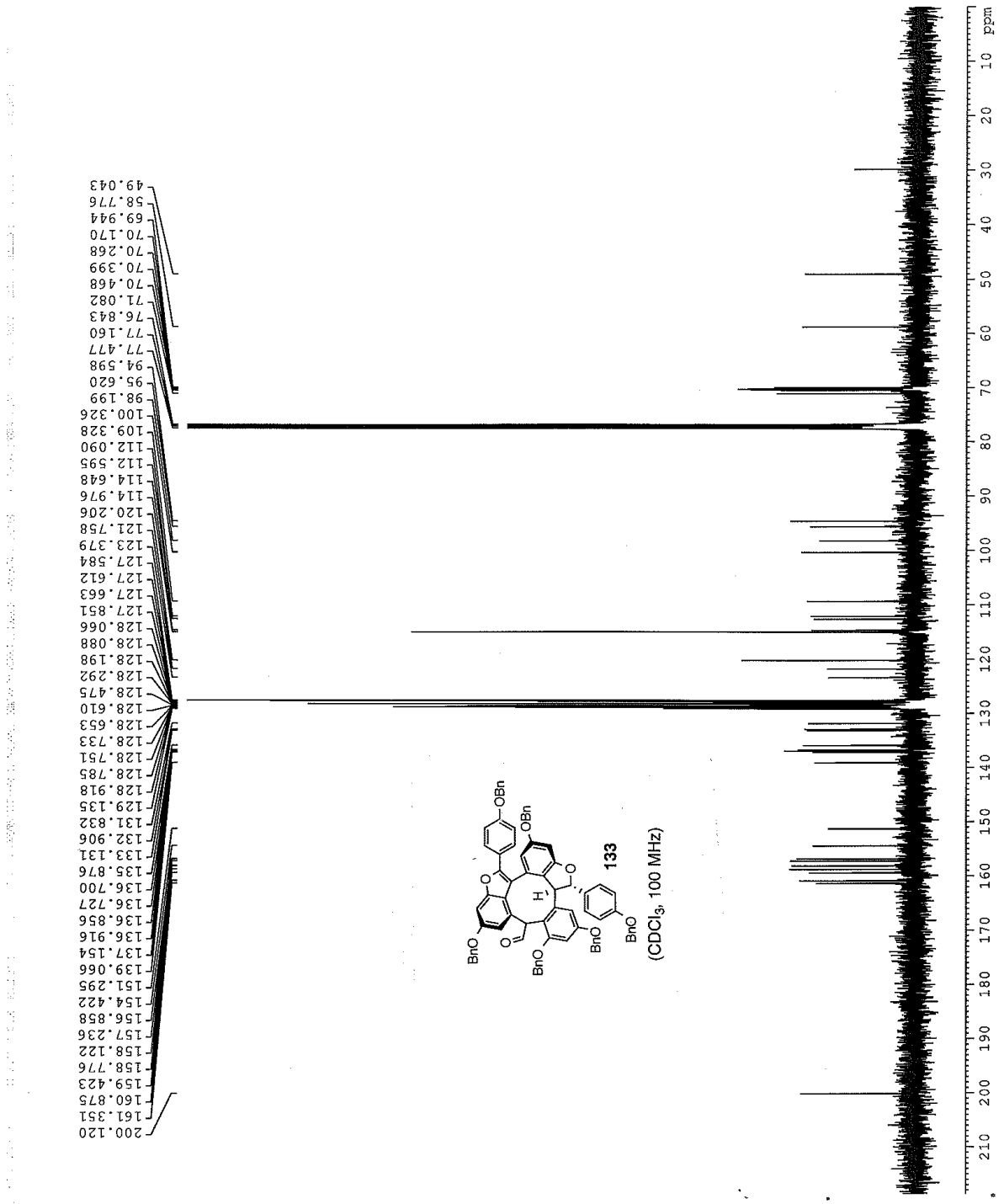

131
(CDCl3, 400 MHz)
OBn
OBn
BnO
BnO
BnO
BnO
OH
ppm

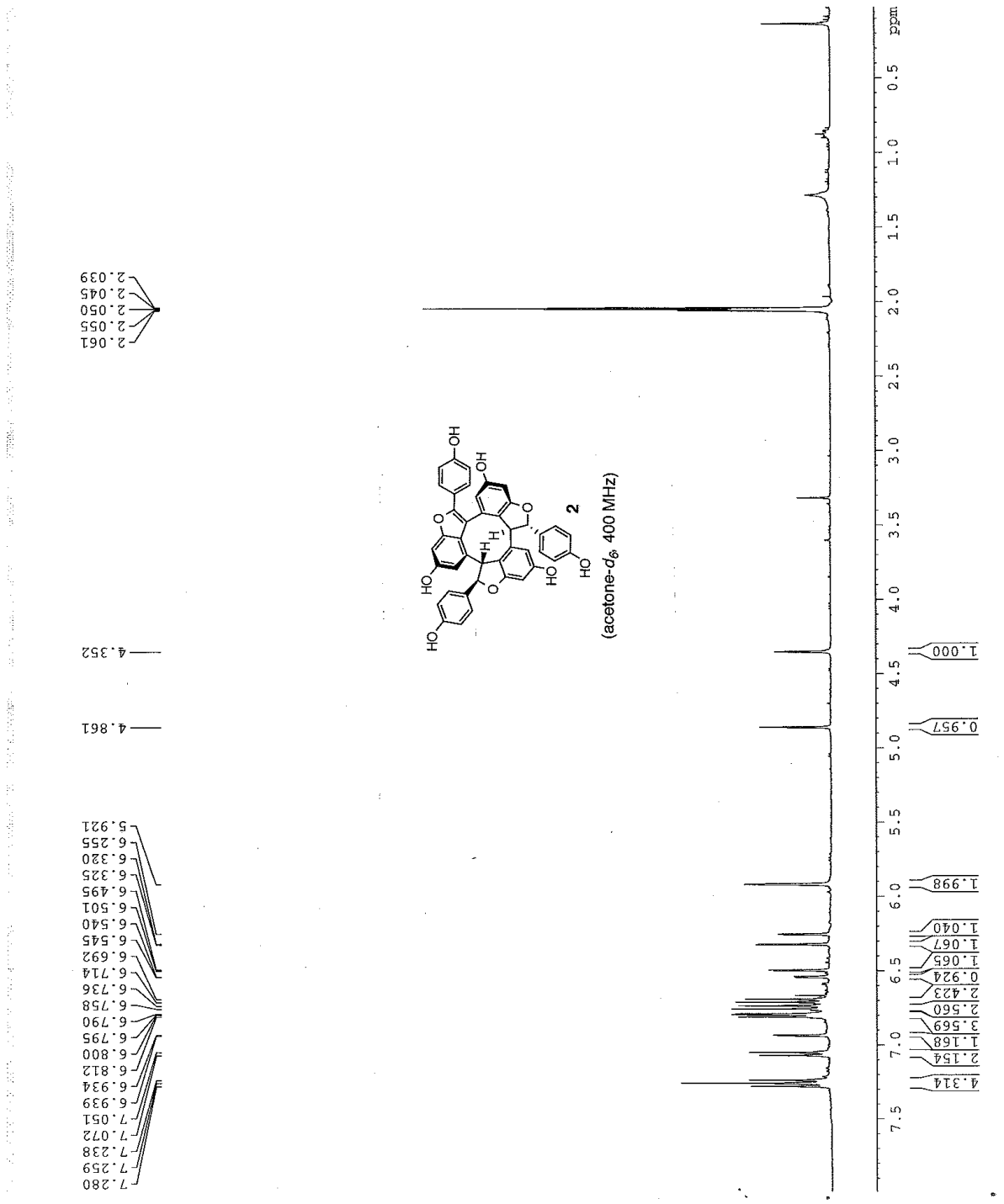

131
(CDCl3, 100 MHz)
ppm

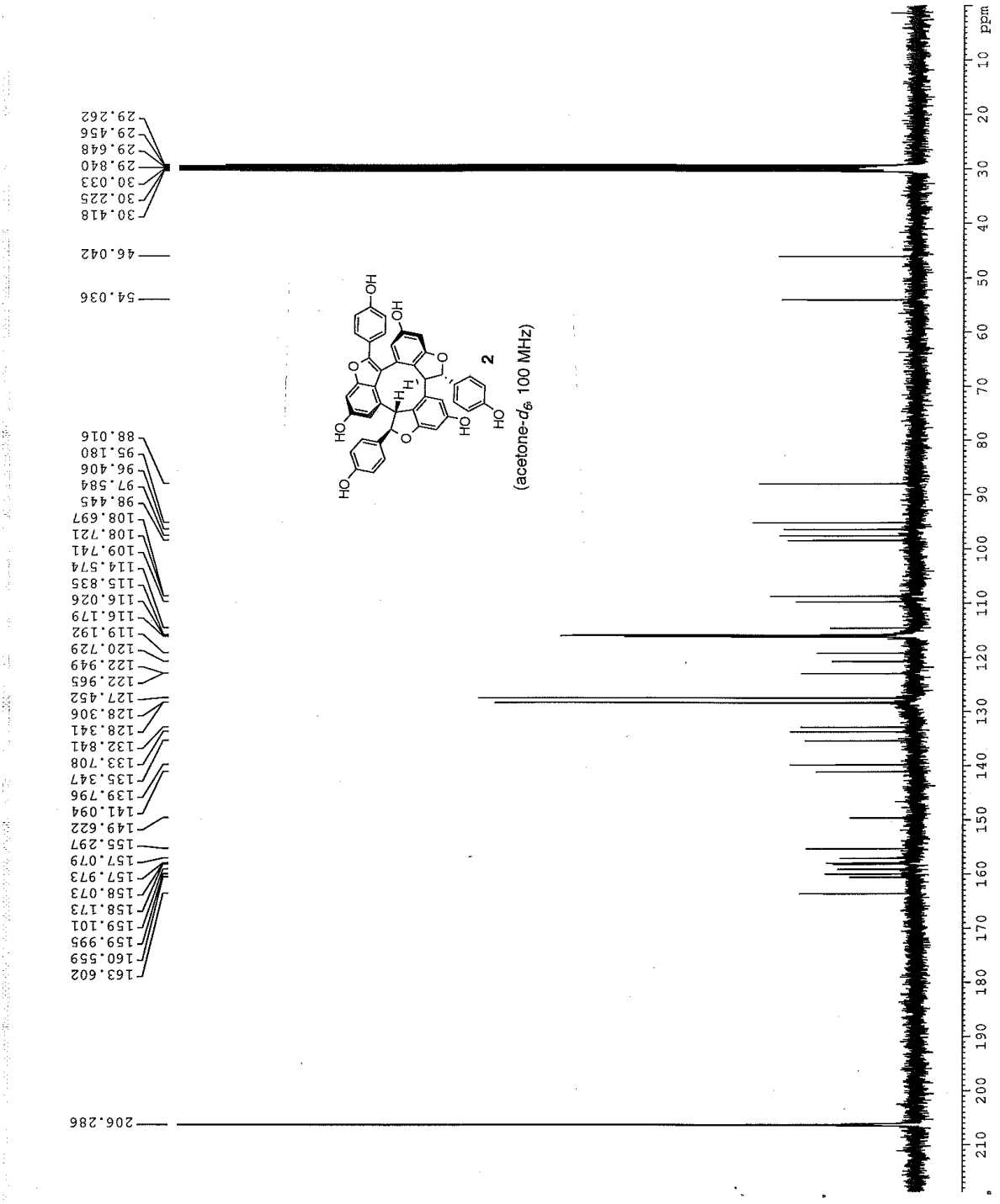

OBn
OBn
BnO
BnO
BnO
BnO
132
(CDCl3, 500 MHz)
ppm

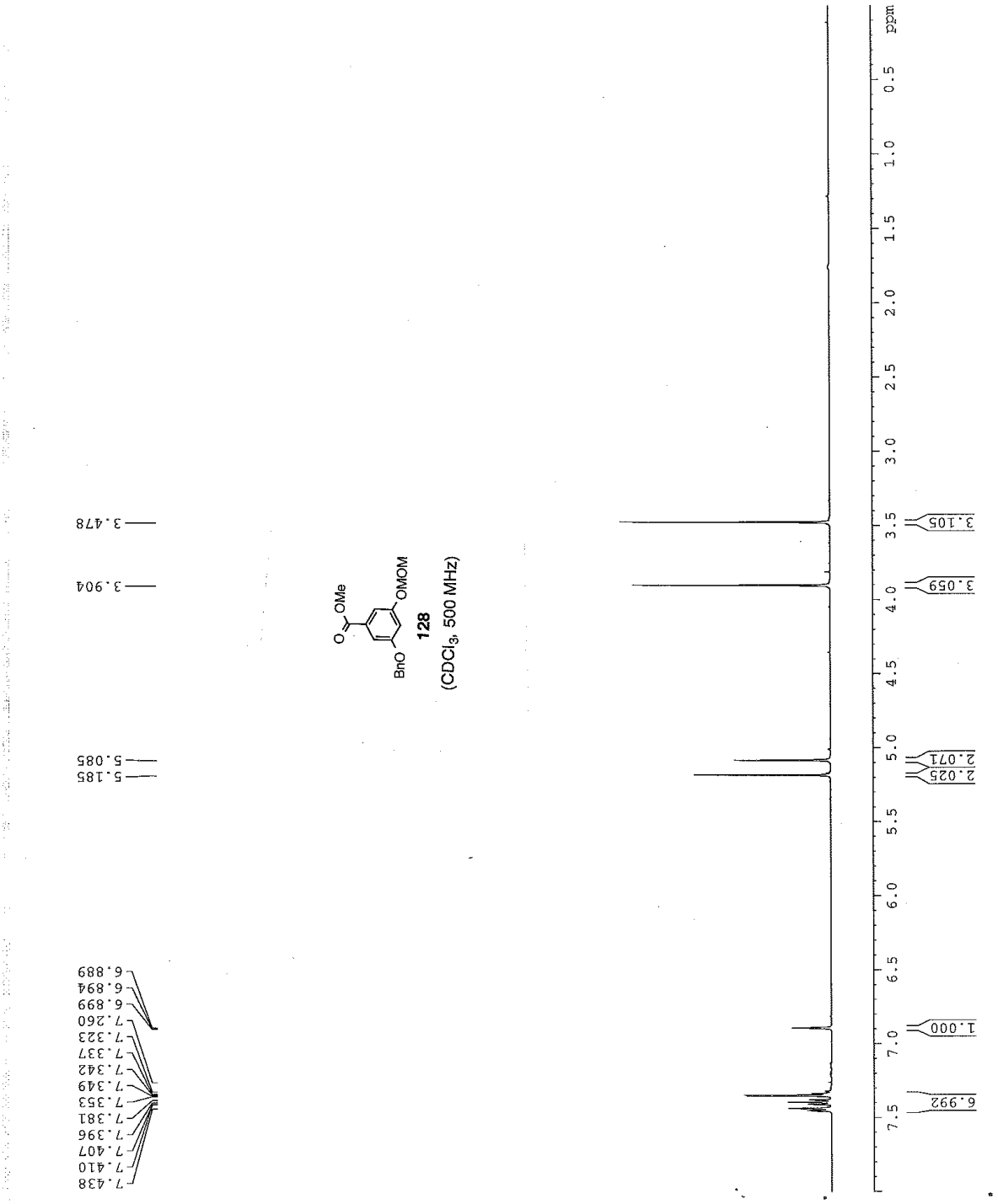

41.494
60.453
69.822
70.104
70.198
70.290
70.339
70.491
76.906
77.160
77.414
93.927
94.555
97.988
100.790
109.459
111.494
113.024
114.737
114.859
115.143
115.367
121.323
122.081
123.613
124.247
127.520
127.587
127.599
127.615
127.674
127.752
127.840
127.975
127.993
128.089
128.158
128.170
128.211
128.336
128.556
128.604
128.646
128.690
128.717
128.755
129.245
131.172
132.588
136.078
136.786
136.859
136.879
136.939
137.293
138.698
138.808
151.412
154.249
156.647
157.248
158.604
158.625
159.318
160.218
OBn
OBn
BnO
BnO
BnO
BnO
132
(CDCl3, 125 MHz)
ppm

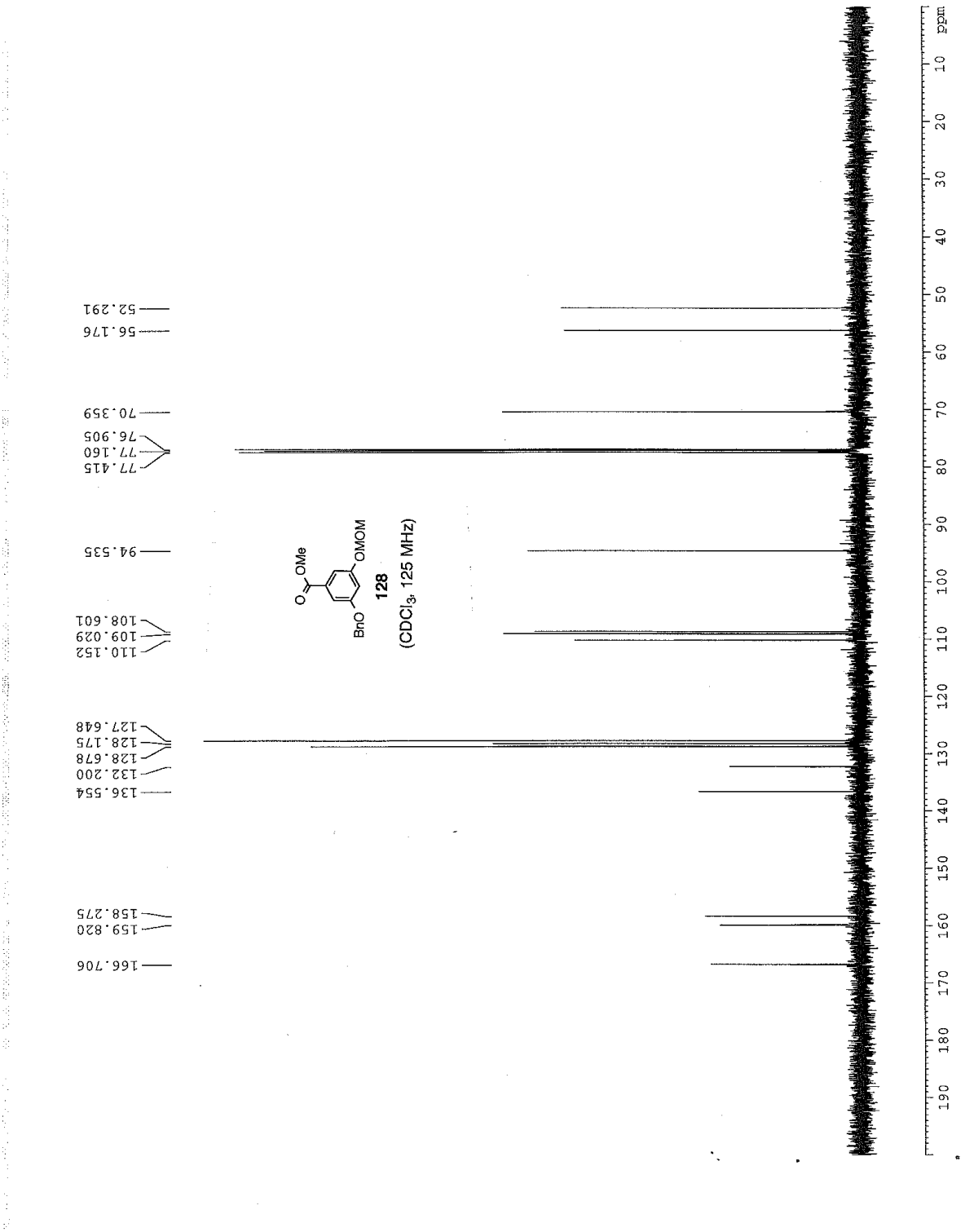

133
(CDCl3, 400 MHz)
OBn
BnO
H
O
ppm

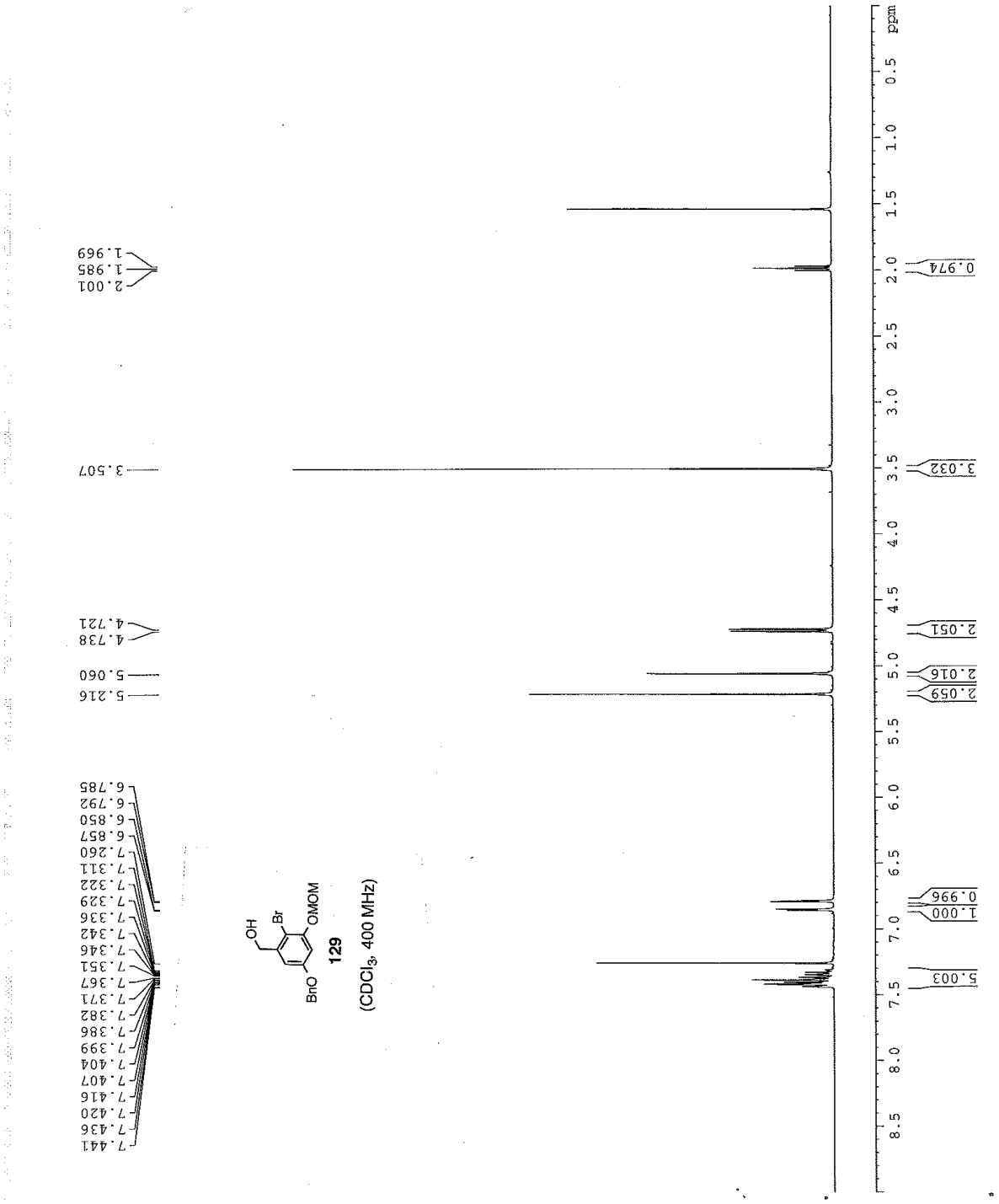

OBn
OBn
BnO
BnO
BnO
BnO
O
O
H
O
133
(CDCl3, 100 MHz)
ppm

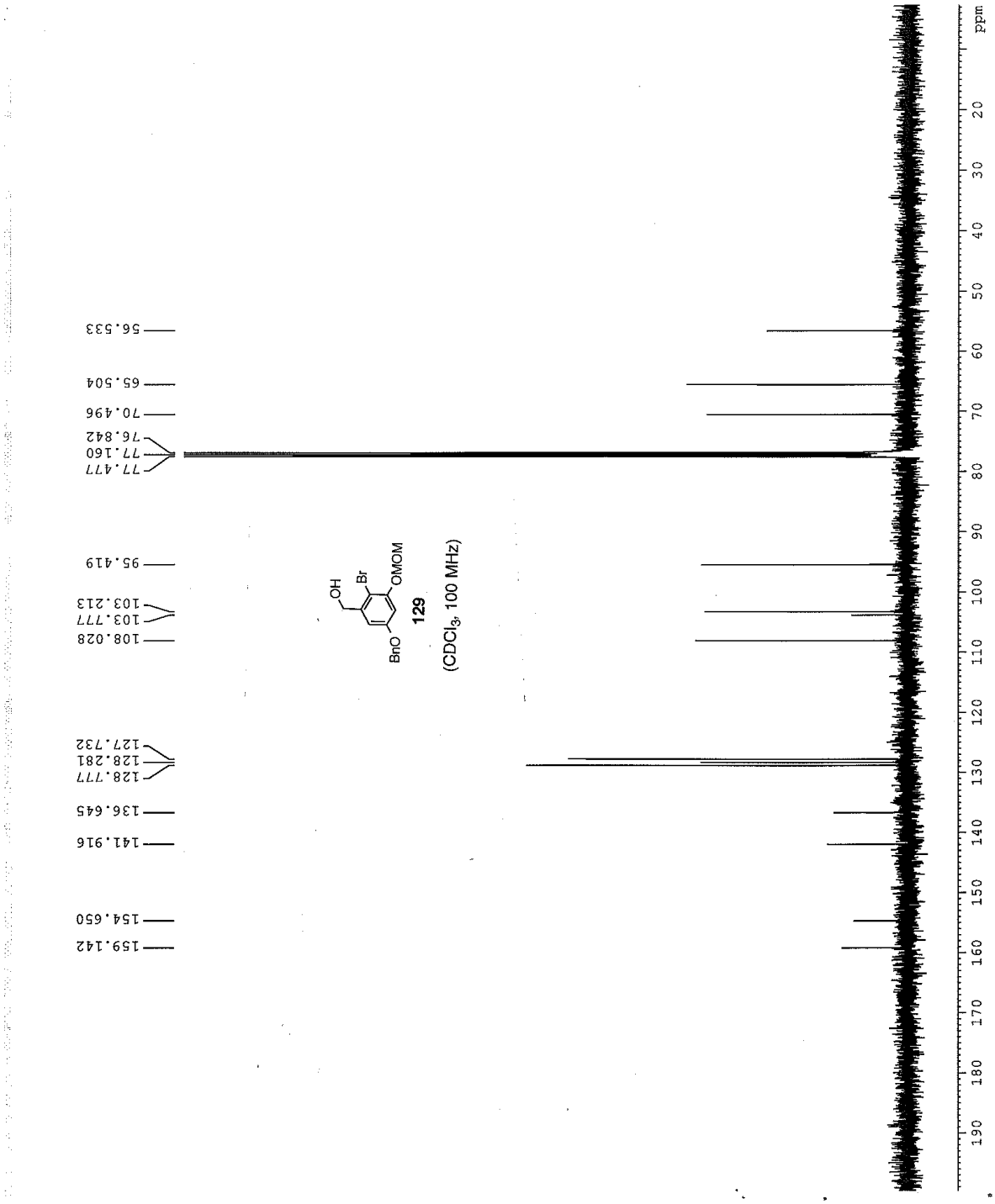

2
(acetone-d_6, 400 MHz)
ppm
7.280
7.259
7.238
7.072
7.051
6.939
6.934
6.812
6.800
6.795
6.790
6.758
6.736
6.714
6.692
6.545
6.540
6.501
6.495
6.325
6.320
6.255
5.921
4.861
4.352
2.061
2.055
2.050
2.045
2.039
4.314
2.154
1.168
3.569
2.560
2.423
0.924
1.065
1.067
1.040
1.998
0.957
1.000

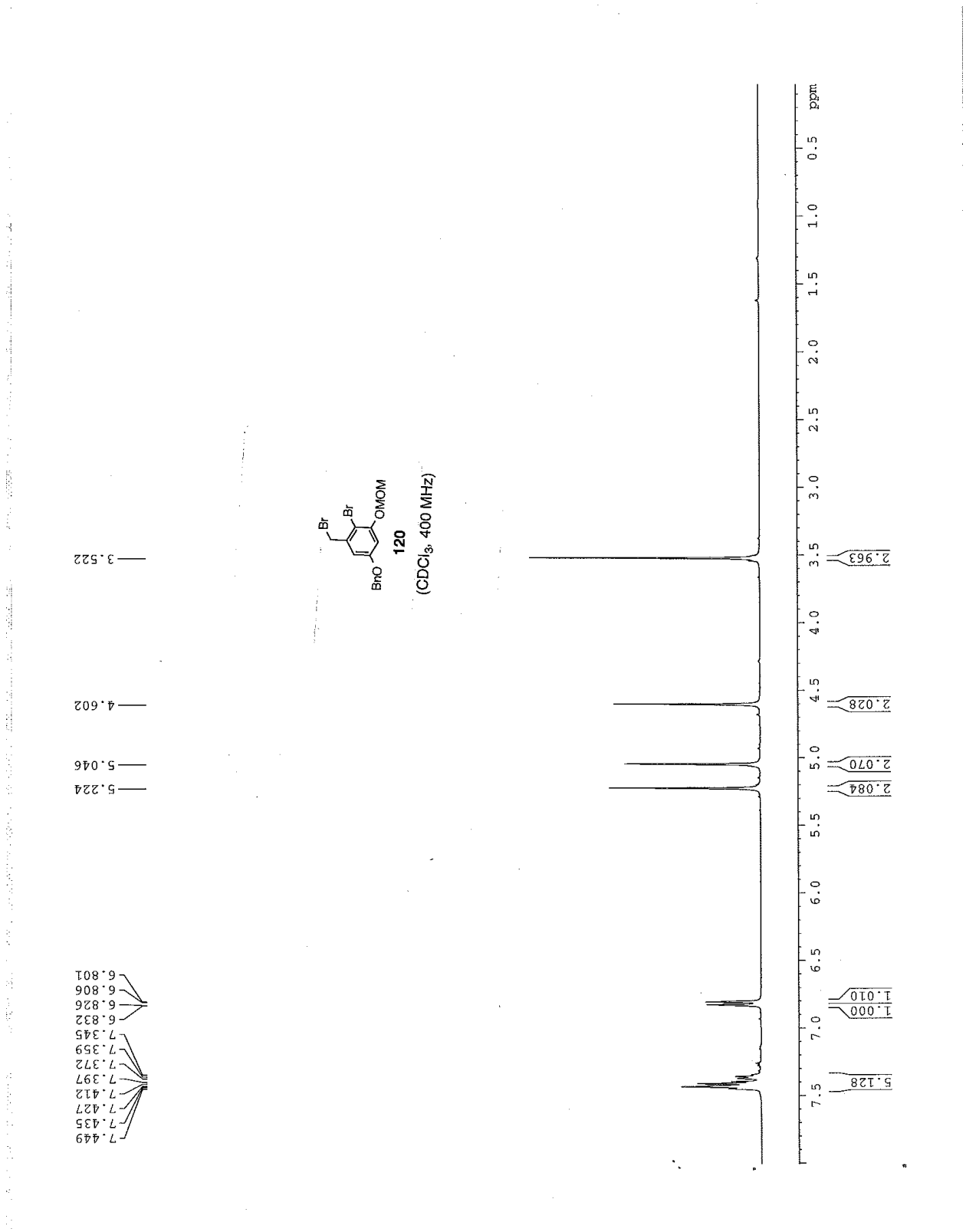

206.286
163.602
160.559
159.995
159.101
158.173
158.073
157.973
157.079
155.297
149.622
141.094
139.796
135.347
133.708
132.841
128.341
128.306
127.452
122.965
122.949
120.729
119.192
116.179
116.026
115.835
114.574
109.741
108.721
108.697
98.445
97.584
96.406
95.180
88.016
54.036
46.042
30.418
30.225
30.033
29.840
29.648
29.456
29.262
OH
OH
HO
HO
HO
HO
O
O
H
H
2
(acetone-d_6, 100 MHz)
ppm

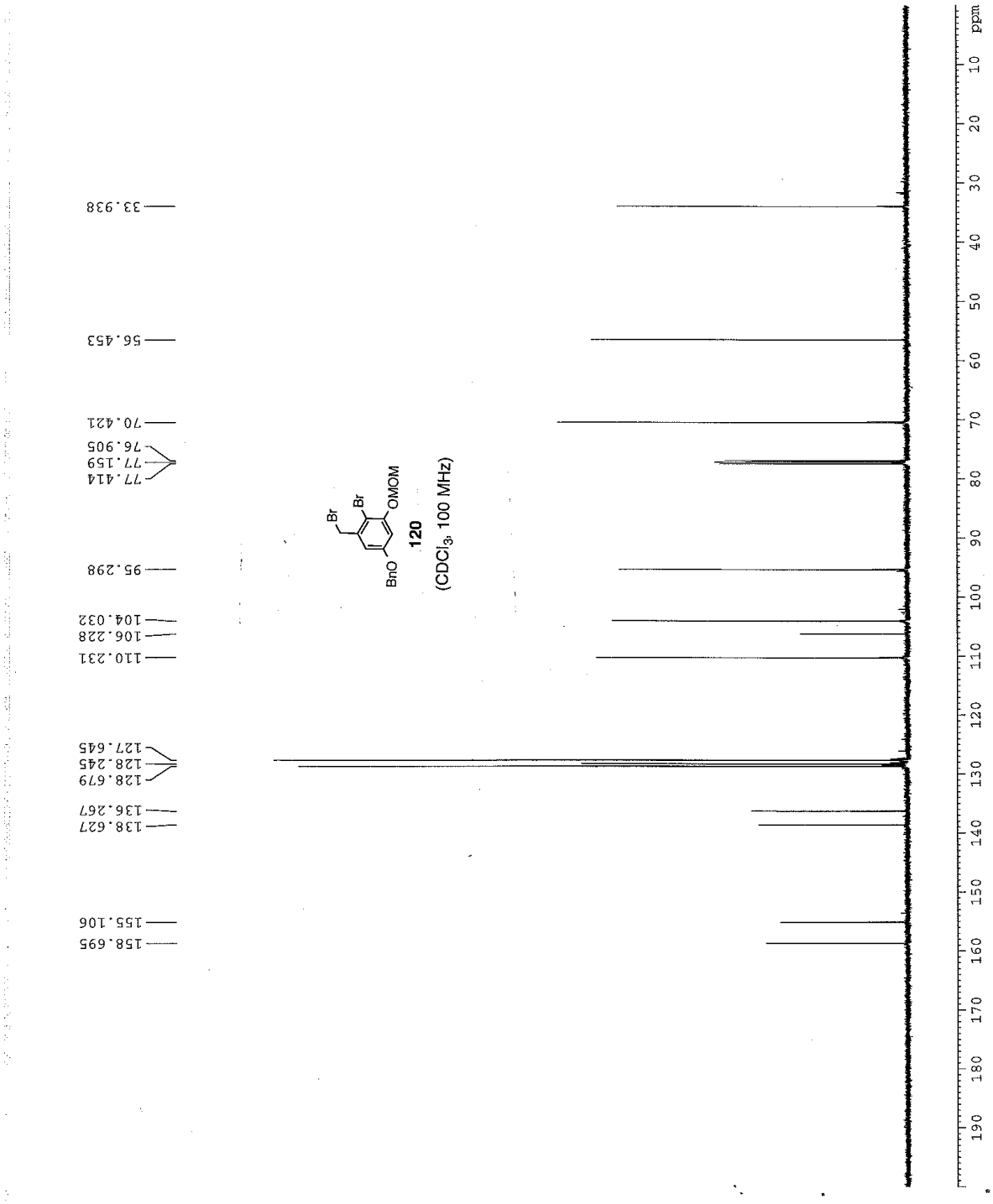

OMe
OMOM
BnO
128
(CDCl3, 500 MHz)
3.478
3.904
5.085
5.185
6.889
6.894
6.899
7.260
7.323
7.337
7.342
7.349
7.353
7.381
7.396
7.407
7.410
7.438
3.105
3.059
2.025
2.071
1.000
6.992
ppm

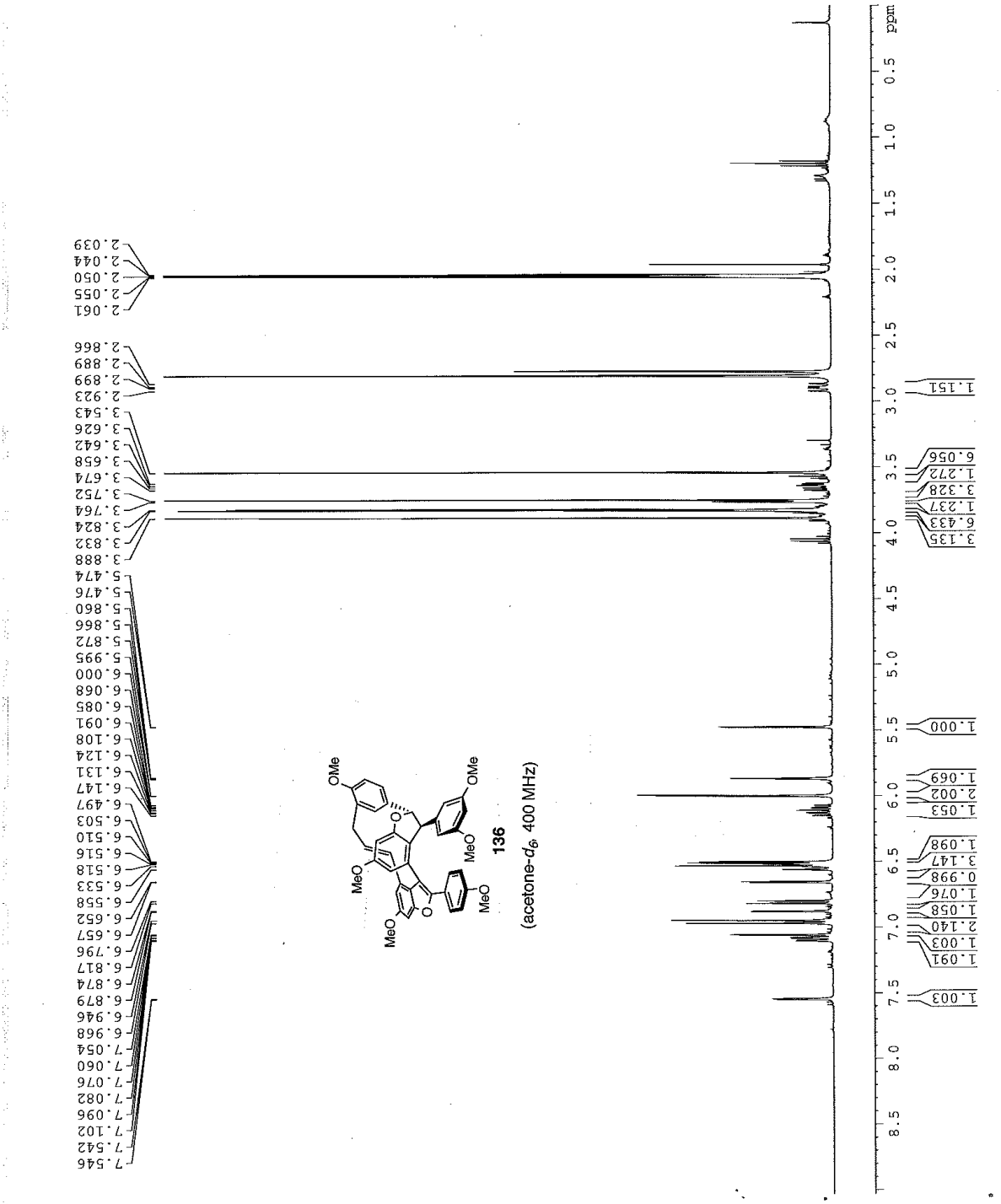

52.291
56.176
70.359
76.905
77.160
77.415
94.535
108.601
109.029
110.152
127.648
128.175
128.678
132.200
136.554
158.275
159.820
166.706
OMe
OMOM
BnO
128
(CDCl3, 125 MHz)
ppm

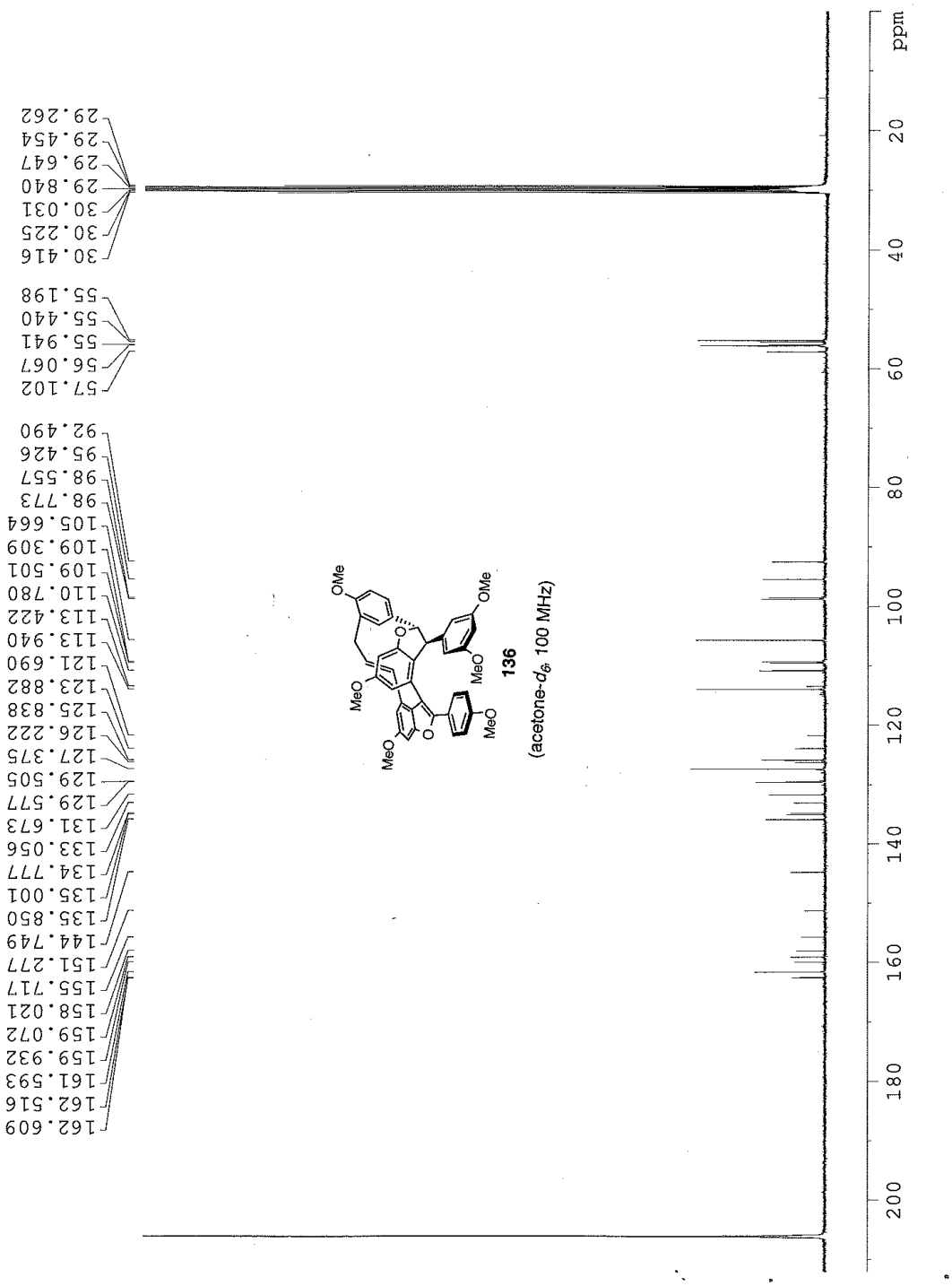

OH
Br
OMOM
BnO
129
(CDCl3, 400 MHz)
7.441
7.436
7.420
7.416
7.407
7.404
7.399
7.386
7.382
7.371
7.367
7.351
7.346
7.342
7.336
7.329
7.322
7.311
7.260
6.857
6.850
6.792
6.785
5.216
5.060
4.738
4.721
3.507
2.001
1.985
1.969
ppm
0.974
3.032
2.051
2.016
2.059
1.000
0.996
5.003

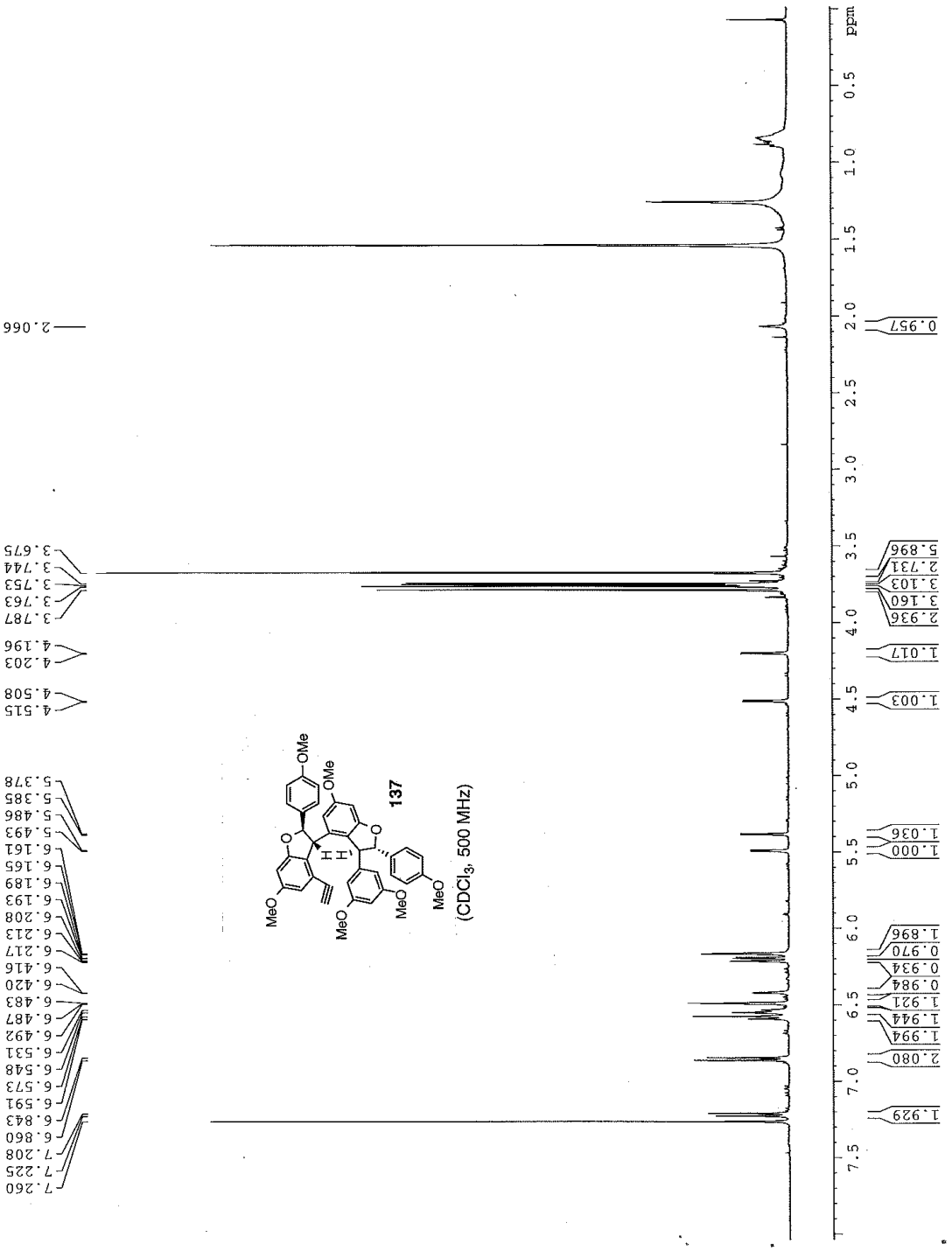

OH
Br
OMOM
BnO
129
(CDCl3, 100 MHz)
56.533
65.504
70.496
76.842
77.160
77.477
95.419
103.213
103.777
108.028
127.732
128.281
128.777
136.645
141.916
154.650
159.142
ppm

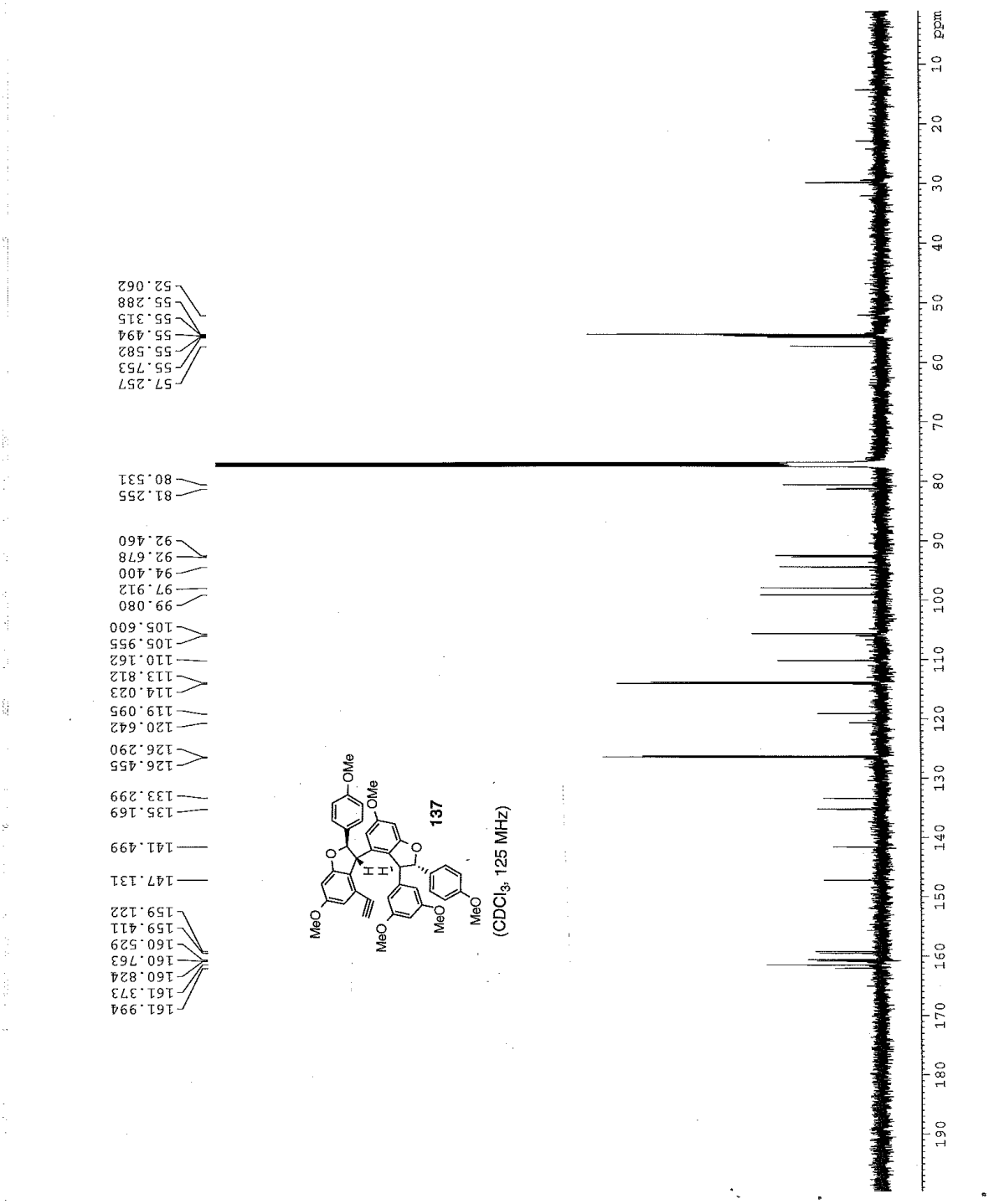

Br
Br
OMOM
BnO
120
(CDCl3, 400 MHz)
3.522
4.602
5.046
5.224
6.801
6.806
6.826
6.832
7.345
7.359
7.372
7.397
7.412
7.427
7.435
7.449
5.128
1.000
1.010
2.070
2.084
2.028
2.963
ppm

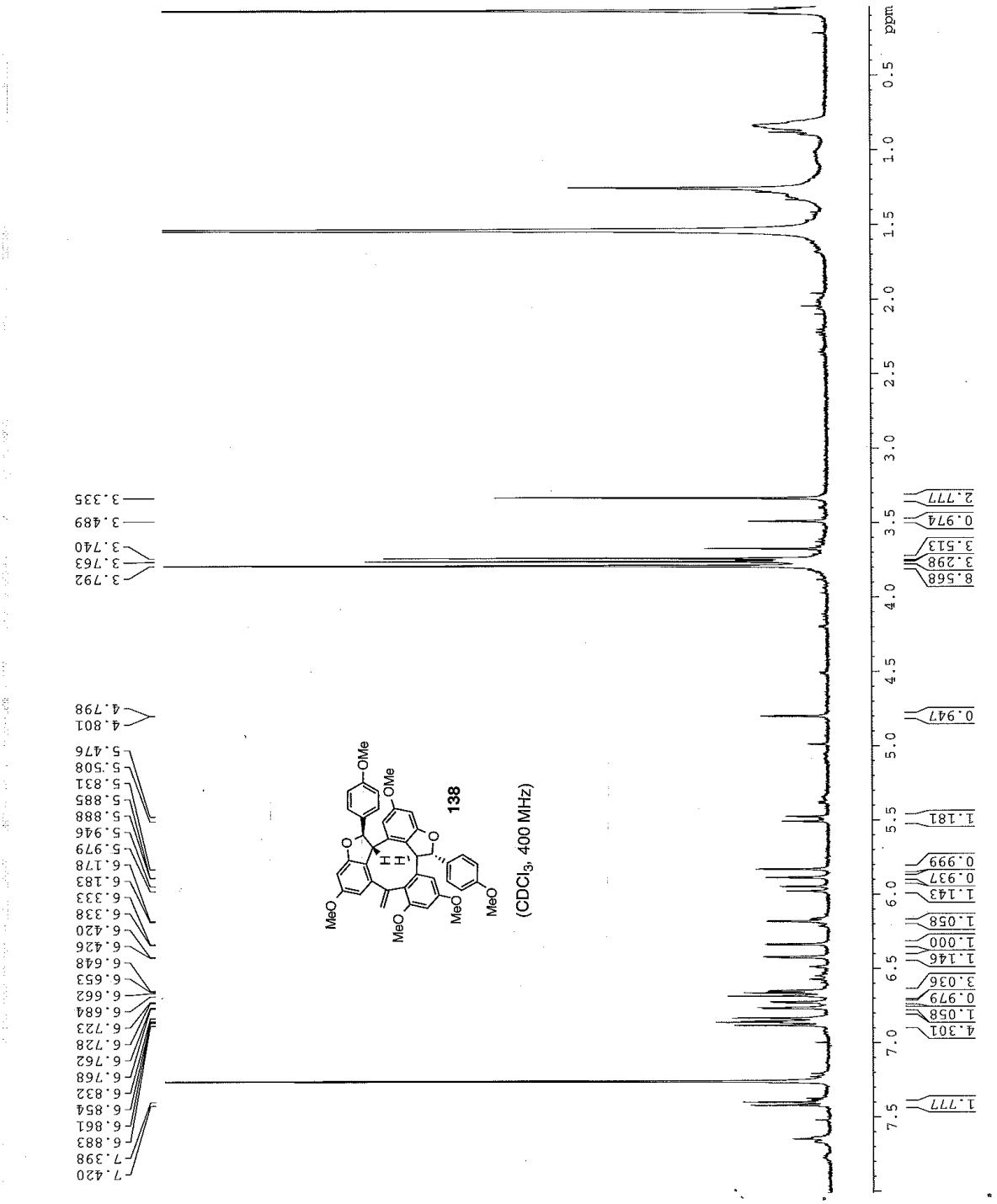

33.938
56.453
70.421
76.905
77.159
77.414
95.298
104.032
106.228
110.231
127.645
128.245
128.679
136.267
138.627
155.106
158.695
Br
Br
OMOM
BnO
120
(CDCl3, 100 MHz)
ppm

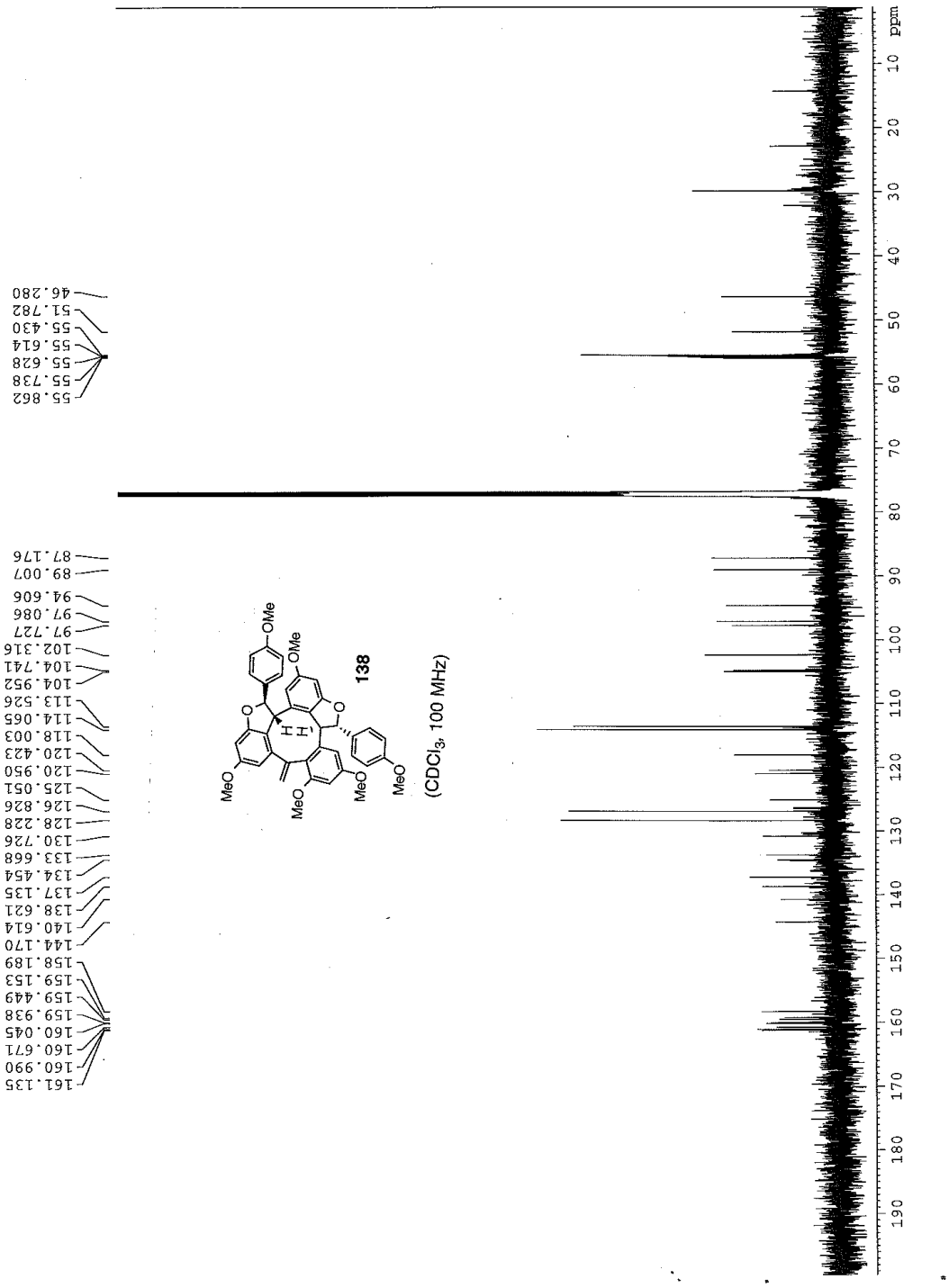

OMe
OMe
MeO
MeO
MeO
MeO
O
O
136
(acetone-d_6, 400 MHz)
ppm

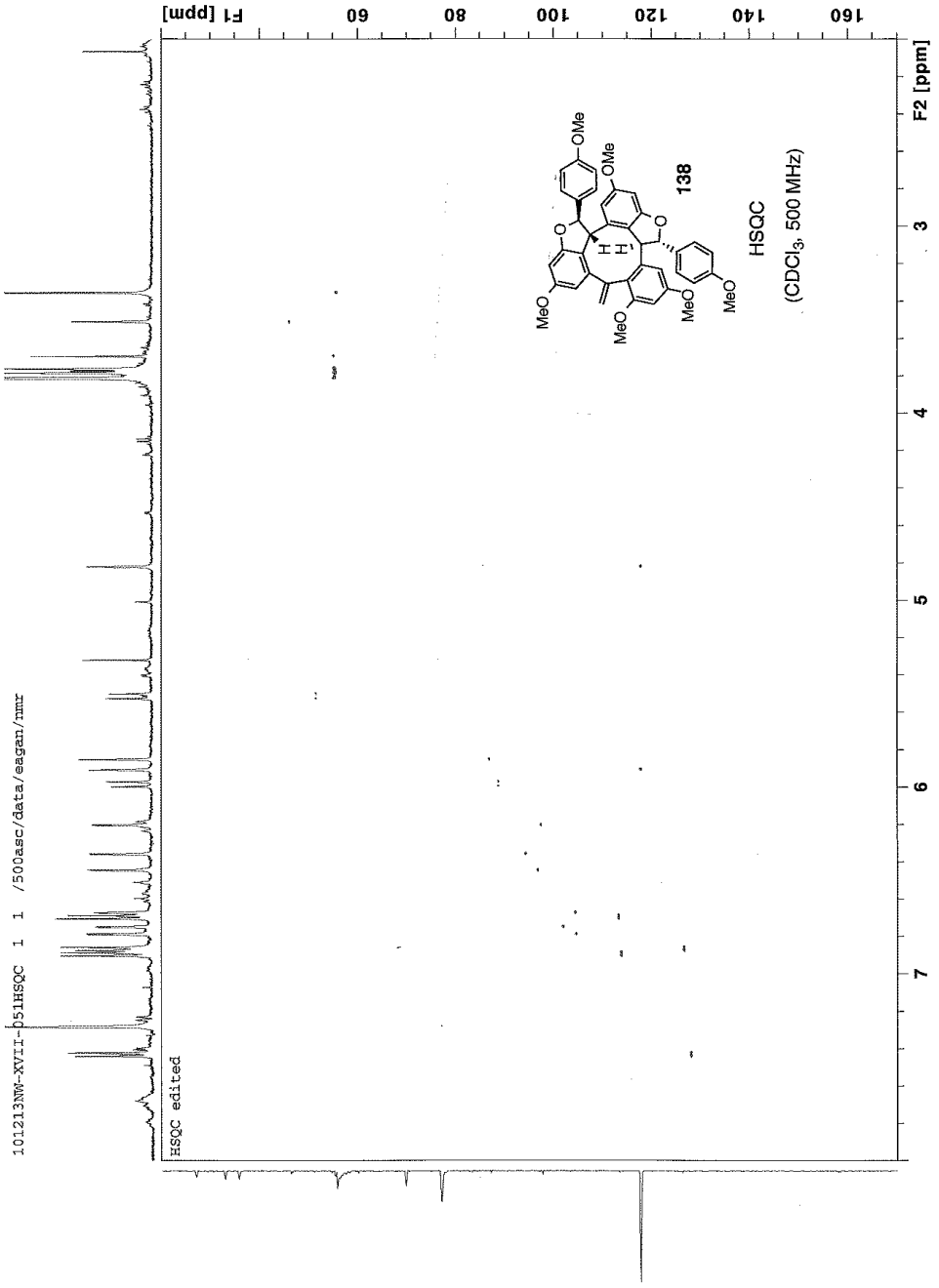

29.262
29.454
29.647
29.840
30.031
30.225
30.416
55.198
55.440
55.941
56.067
57.102
92.490
95.426
98.557
98.773
105.664
109.309
109.501
110.780
113.422
113.940
121.690
123.882
125.838
126.222
127.375
129.505
129.577
131.673
133.056
134.777
135.001
135.850
144.749
151.277
155.717
158.021
159.072
159.932
161.593
162.516
162.609
OMe
OMe
MeO
MeO
MeO
MeO
O
O
136
(acetone-d_6, 100 MHz)
ppm
20
40
60
80
100
120
140
160
180
200

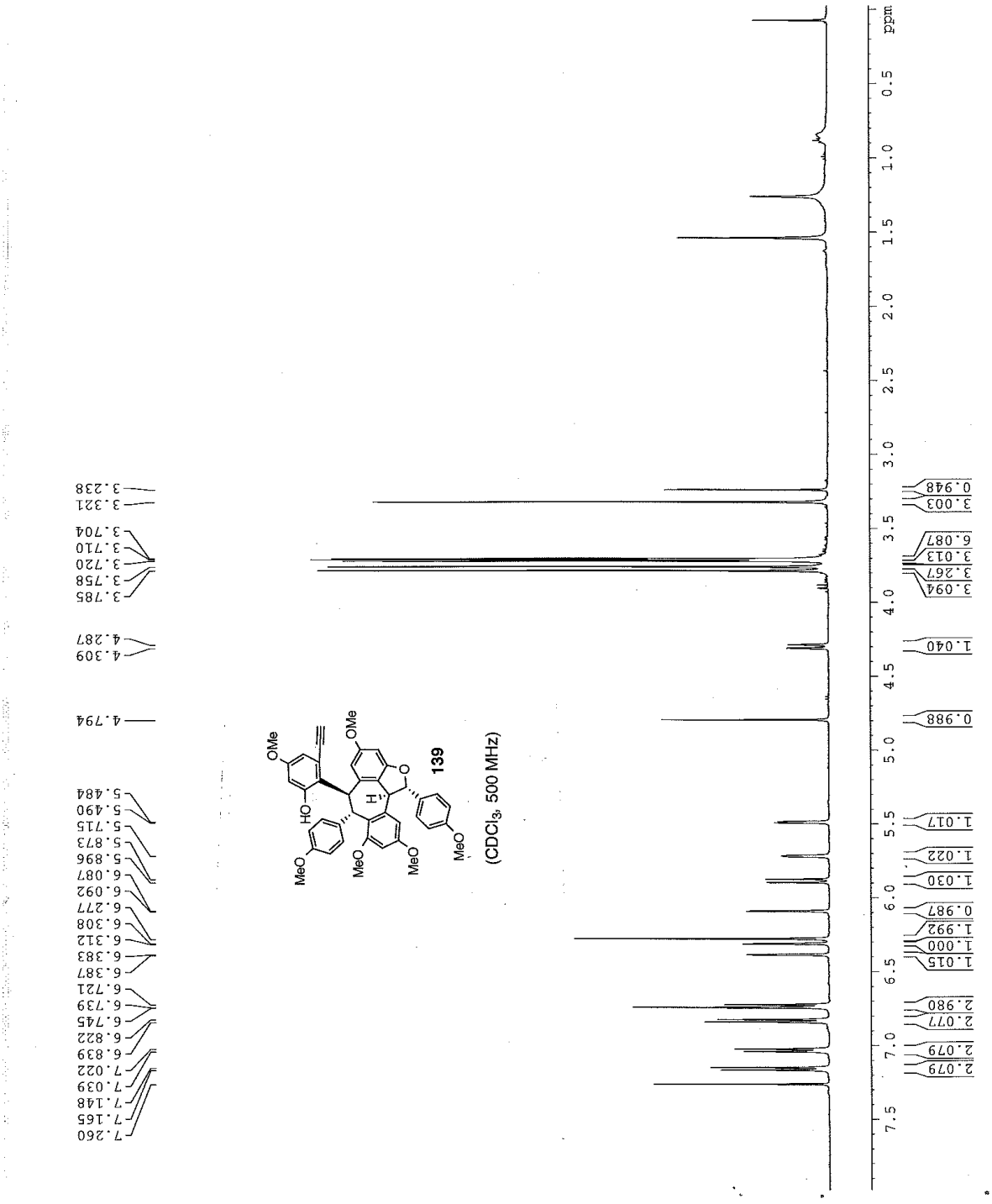

137
(CDCl3, 500 MHz)
OMe
MeO
ppm


161.994
161.373
160.824
160.763
160.529
159.411
159.122
147.131
141.499
135.169
133.299
126.455
126.290
120.642
119.095
114.023
113.812
110.162
105.955
105.600
99.080
97.912
94.400
92.678
92.460
81.255
80.531
57.257
55.753
55.582
55.494
55.315
55.288
52.062
OMe
OMe
MeO
MeO
MeO
MeO
137
(CDCl3, 125 MHz)
ppm


138
(CDCl3, 400 MHz)
MeO
OMe
H
H'
ppm


OMe
OMe
MeO
MeO
MeO
MeO
H
H
138
(CDCl3, 100 MHz)
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
46.280
51.782
55.430
55.614
55.628
55.738
55.862
87.176
89.007
94.606
97.086
97.727
102.316
104.741
104.952
113.526
114.065
118.003
120.423
120.950
125.051
126.826
128.228
130.726
133.668
134.454
137.135
138.621
140.614
144.170
158.189
159.153
159.449
159.938
160.045
160.671
160.990
161.135


101213NM-XVII-051HSQC 1 1 /500asc/data/eagan/nmr
HSQC edited
F1 [ppm]
F2 [ppm]
OMe
OMe
MeO
MeO
MeO
MeO
MeO
H
H'
138
HSQC
(CDCl3, 500 MHz)


OMe
OMe
HO
MeO
MeO
MeO
MeO
H
O
139
(CDCl3, 500 MHz)
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
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1.000
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2.079
2.079
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3.720
3.758
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5.873
5.896
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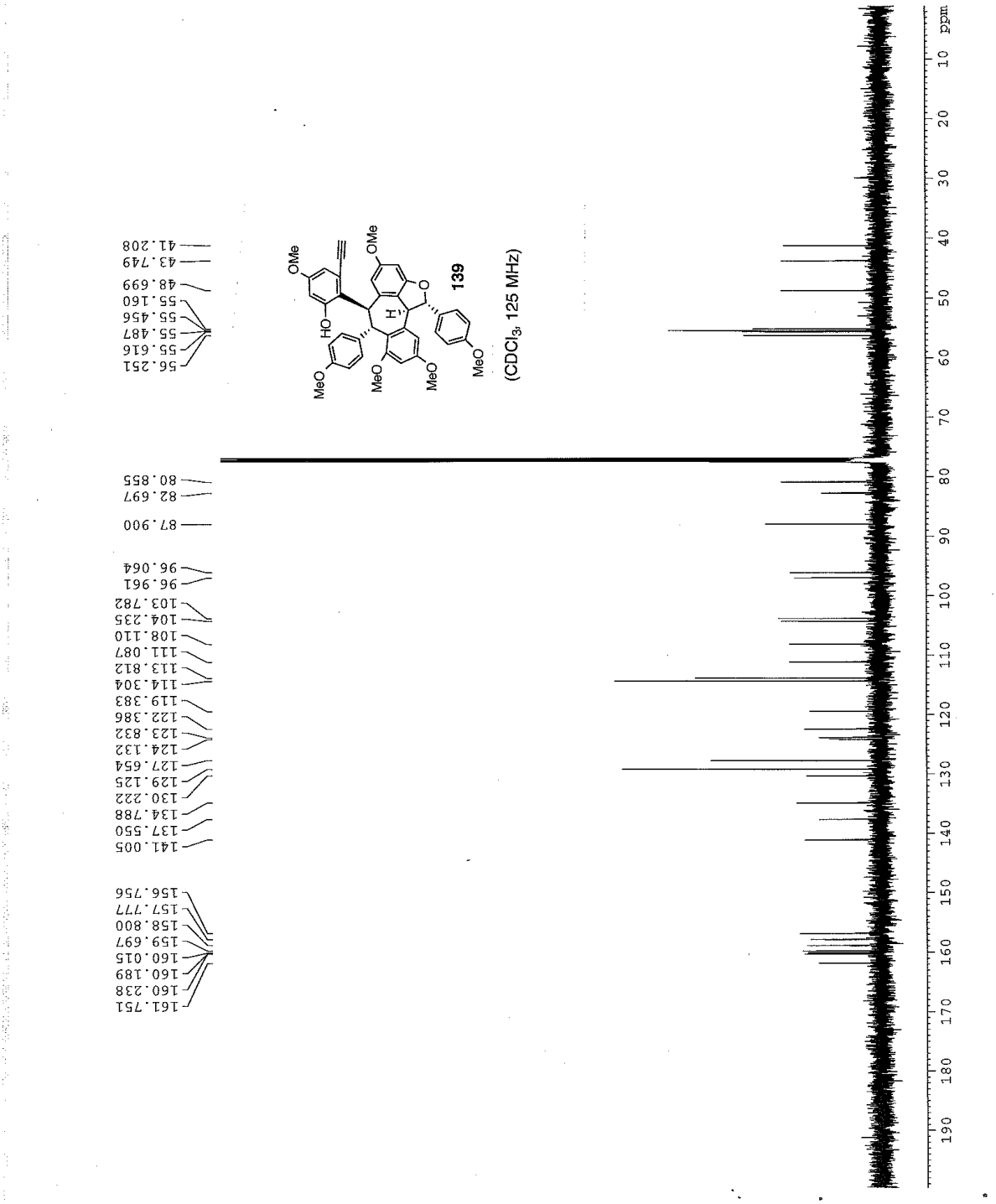
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111.087
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160.015
160.189
160.238
161.751
OMe
OMe
HO
MeO
MeO
MeO
MeO
H1'
O
139
(CDCl3, 125 MHz)
ppm
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40
50
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80
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120
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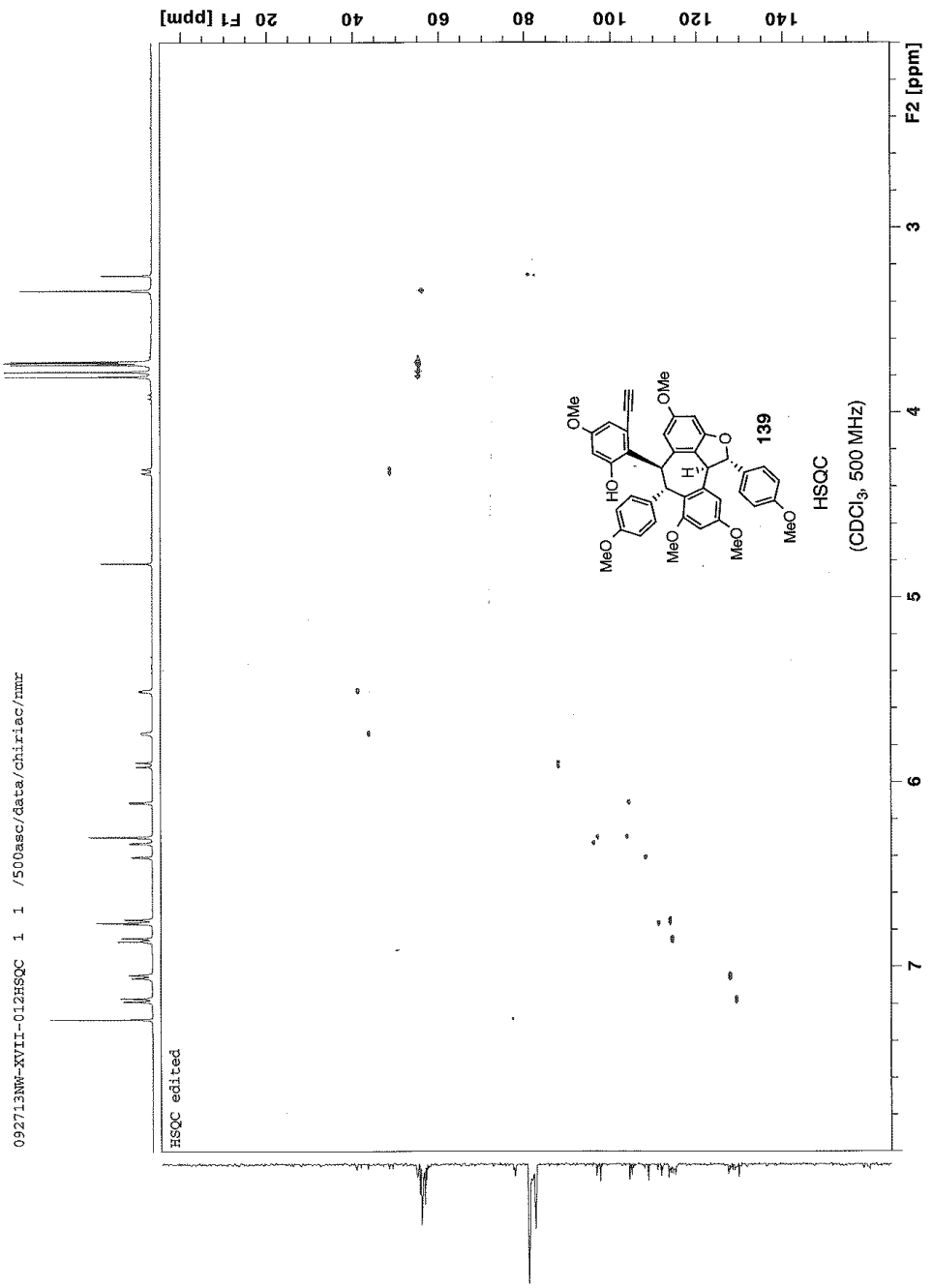
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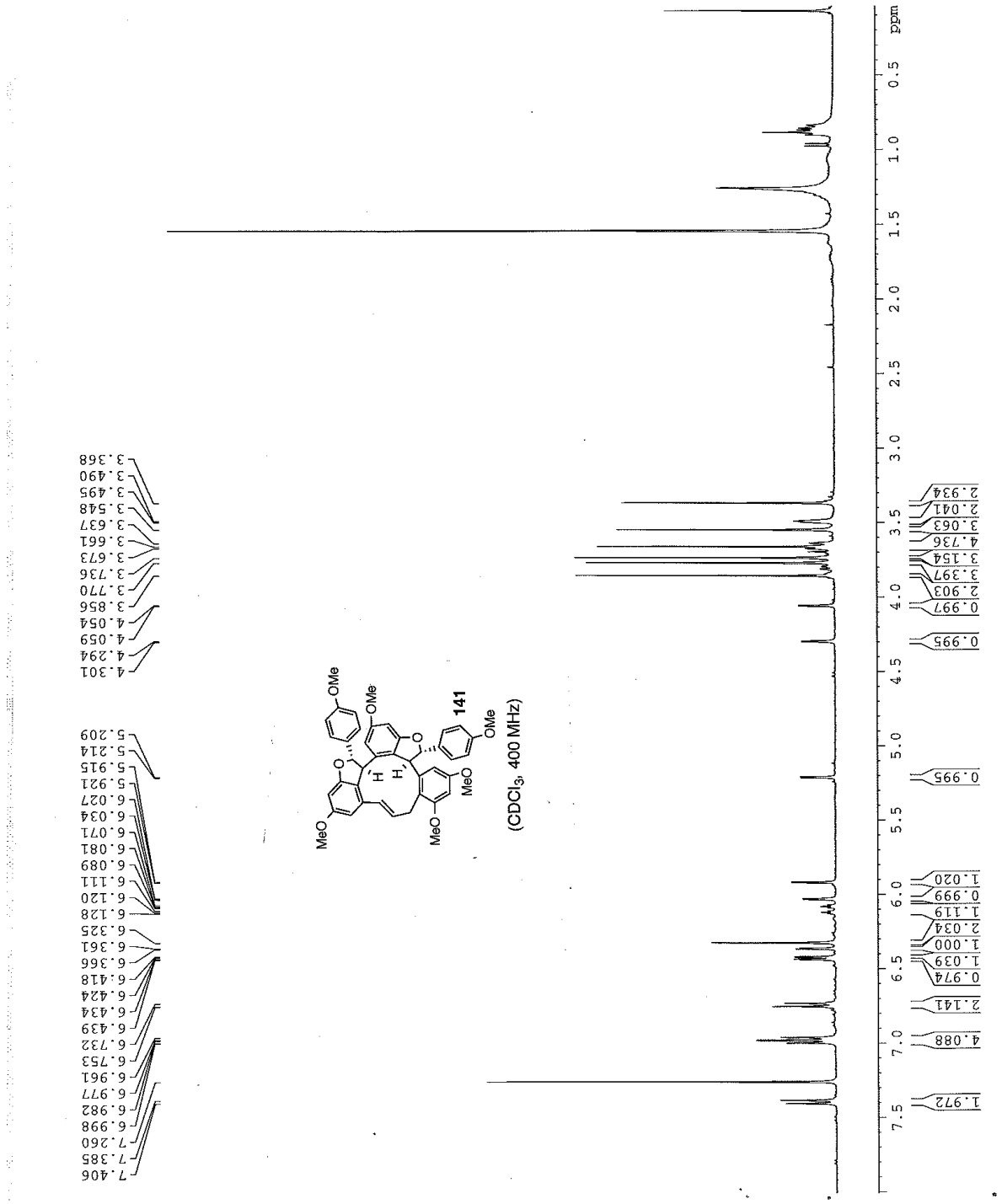
HO
MeO
MeO
MeO
MeO
H
O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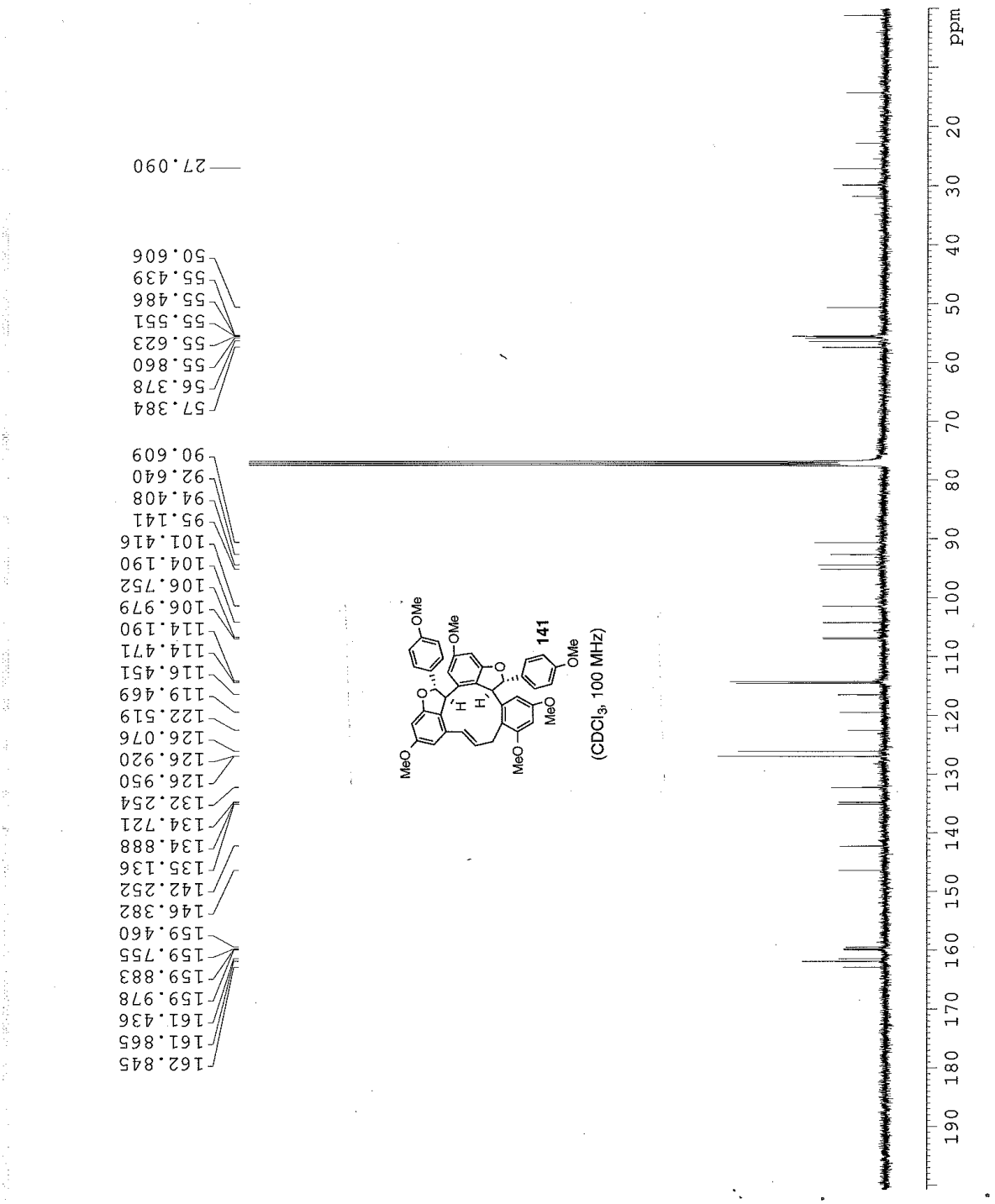
OMe
H
H
ppm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101.416
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106.979
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126.950
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134.888
135.136
142.252
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159.883
159.978
161.436
161.865
162.845
OMe
OMe
OMe
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MeO
MeO
H
H
141
(CDCl3, 100 MHz)
ppm
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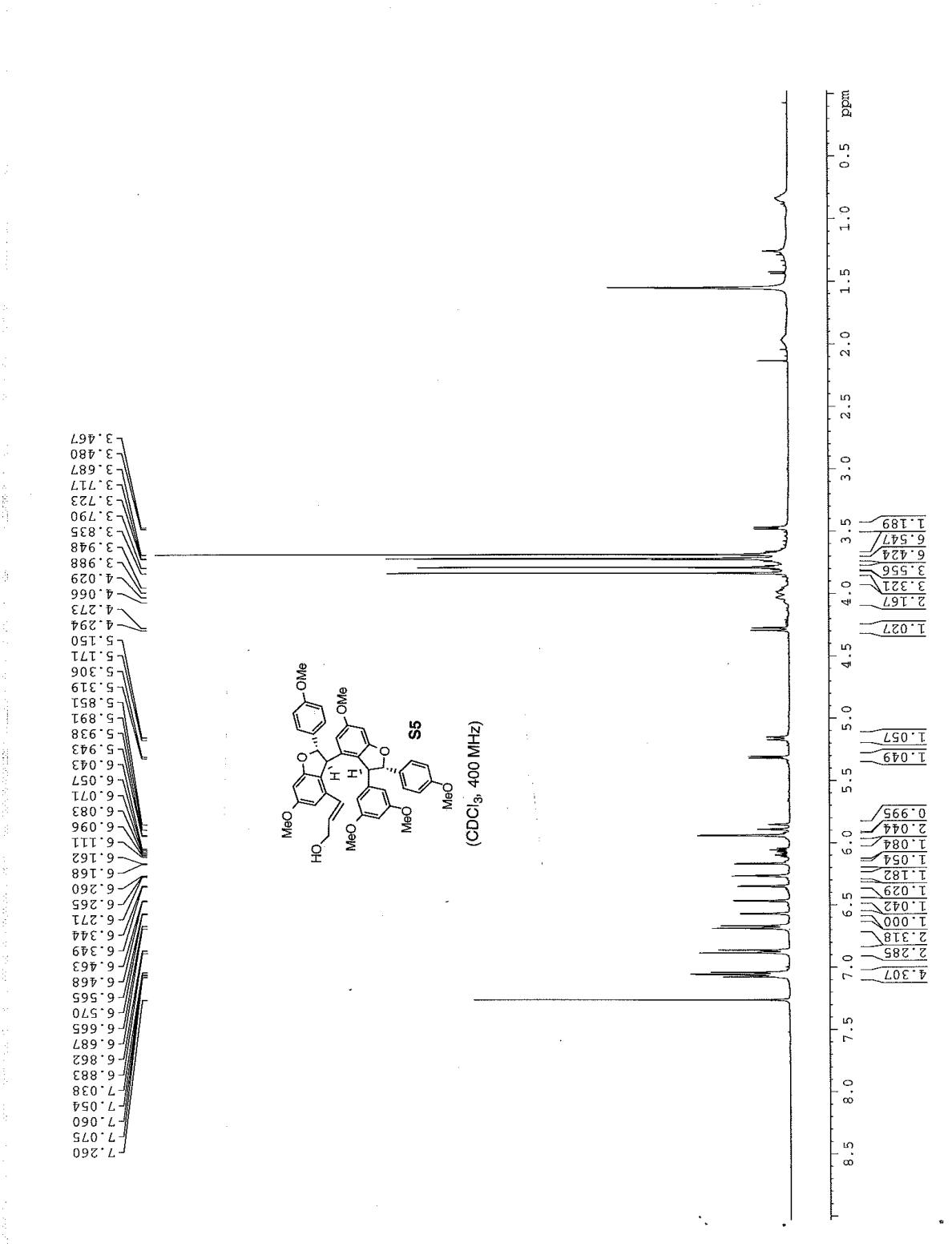
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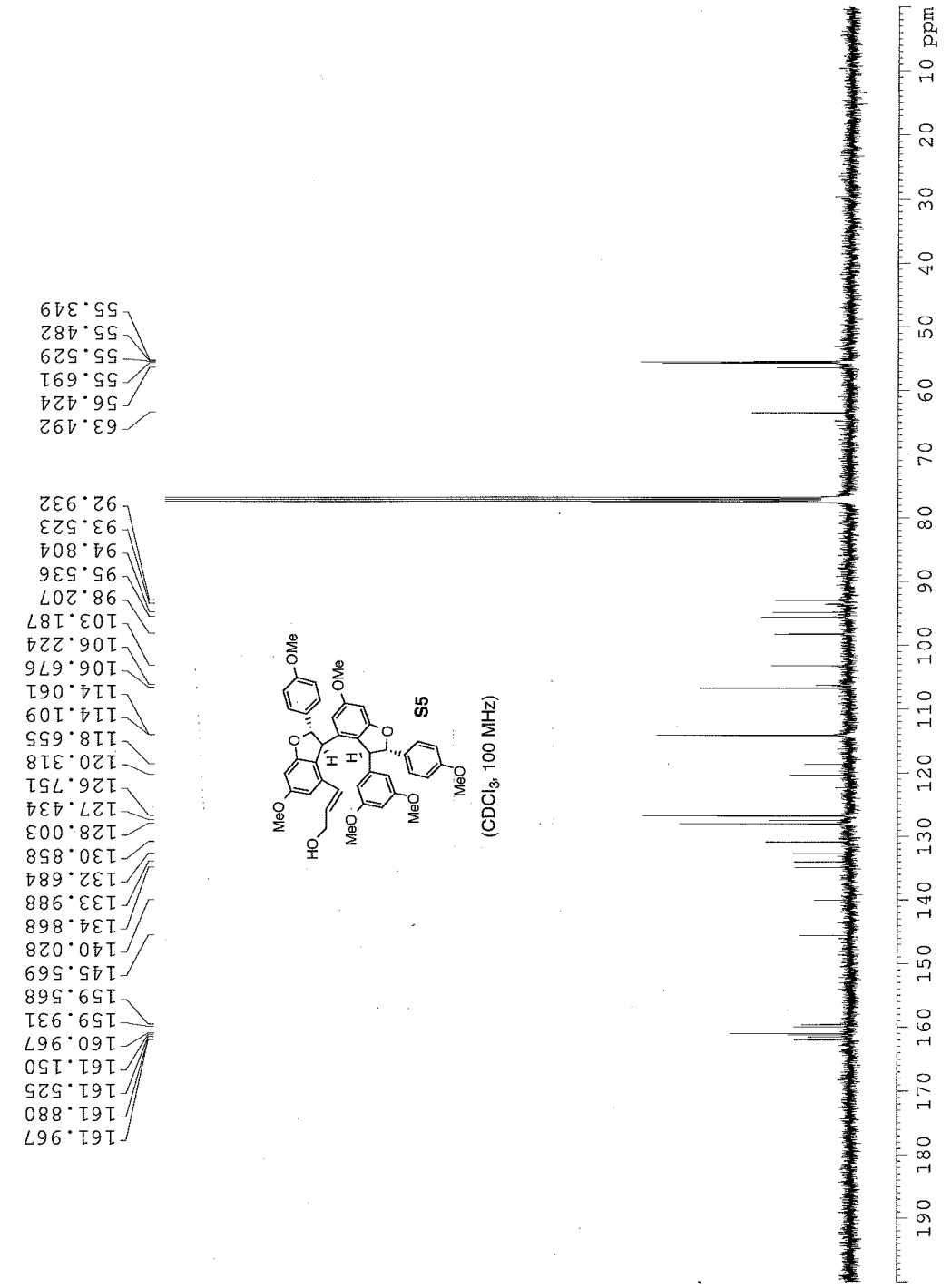
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MeO
MeO
MeO
HO
H'
H'
S5
(CDCl3, 100 MHz)
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132.684
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140.028
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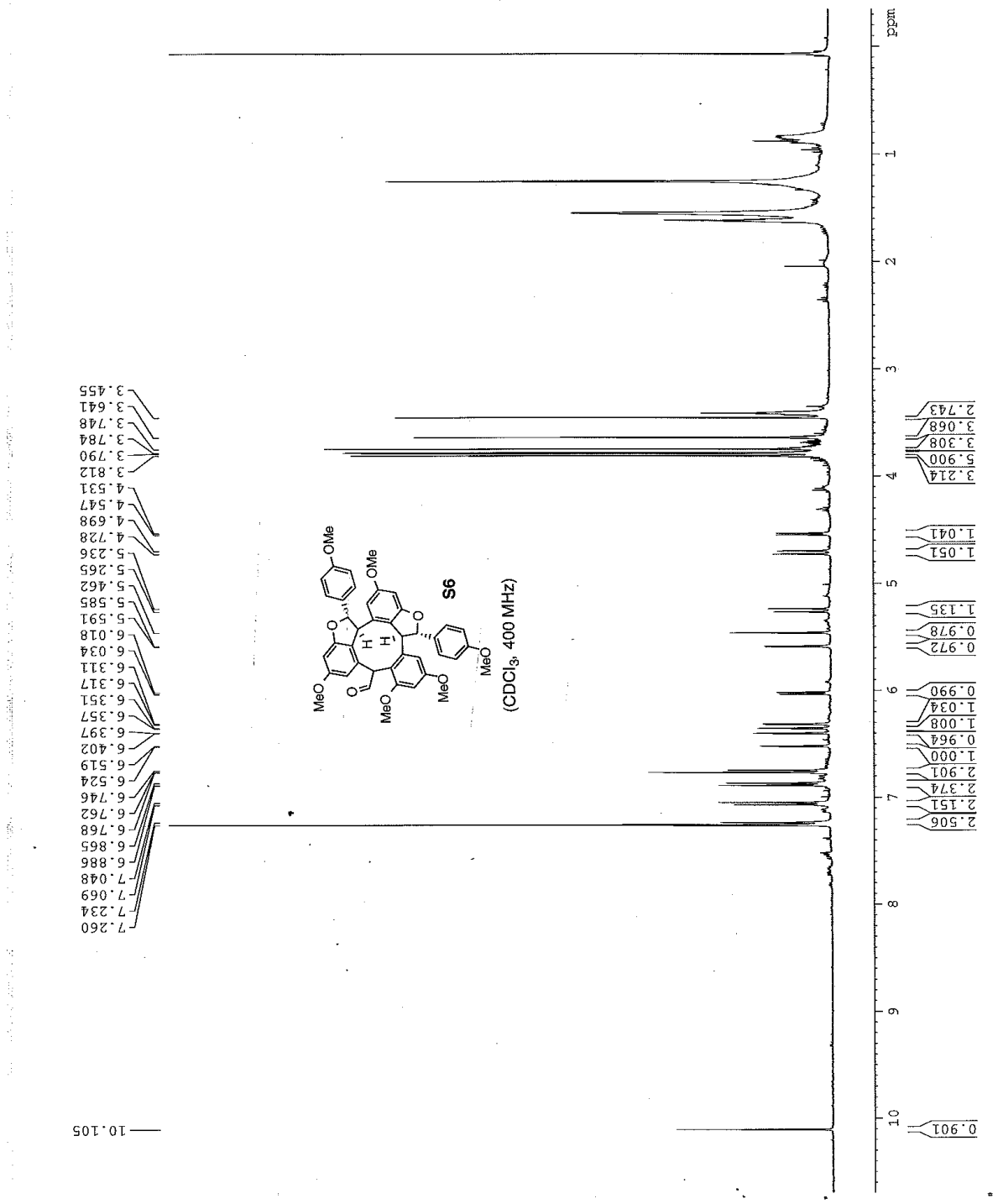
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H
O
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4.547
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3.784
3.748
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2.151
2.374
2.901
1.000
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1.008
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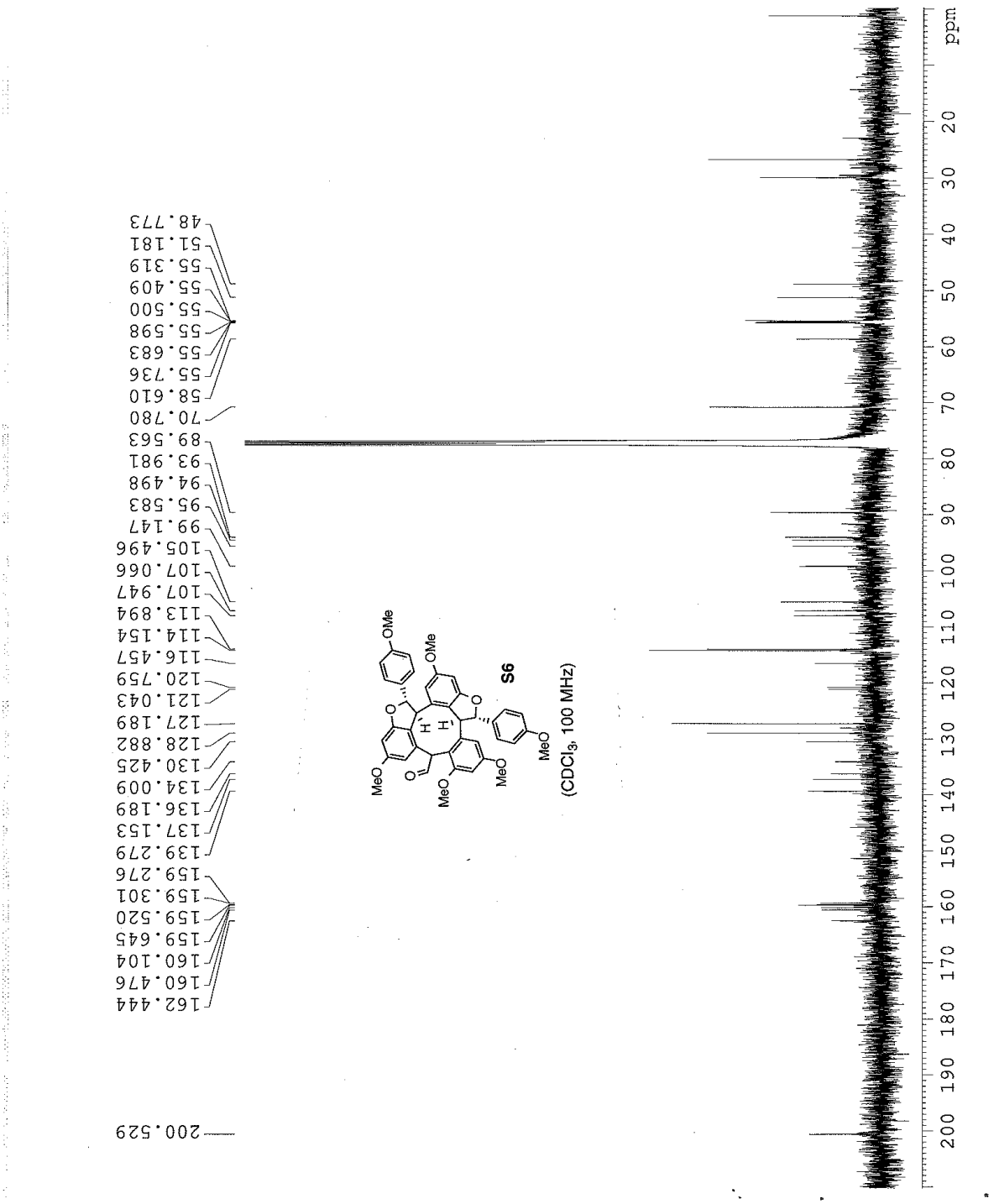
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93.981
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55.736
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55.500
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MeO
MeO
MeO
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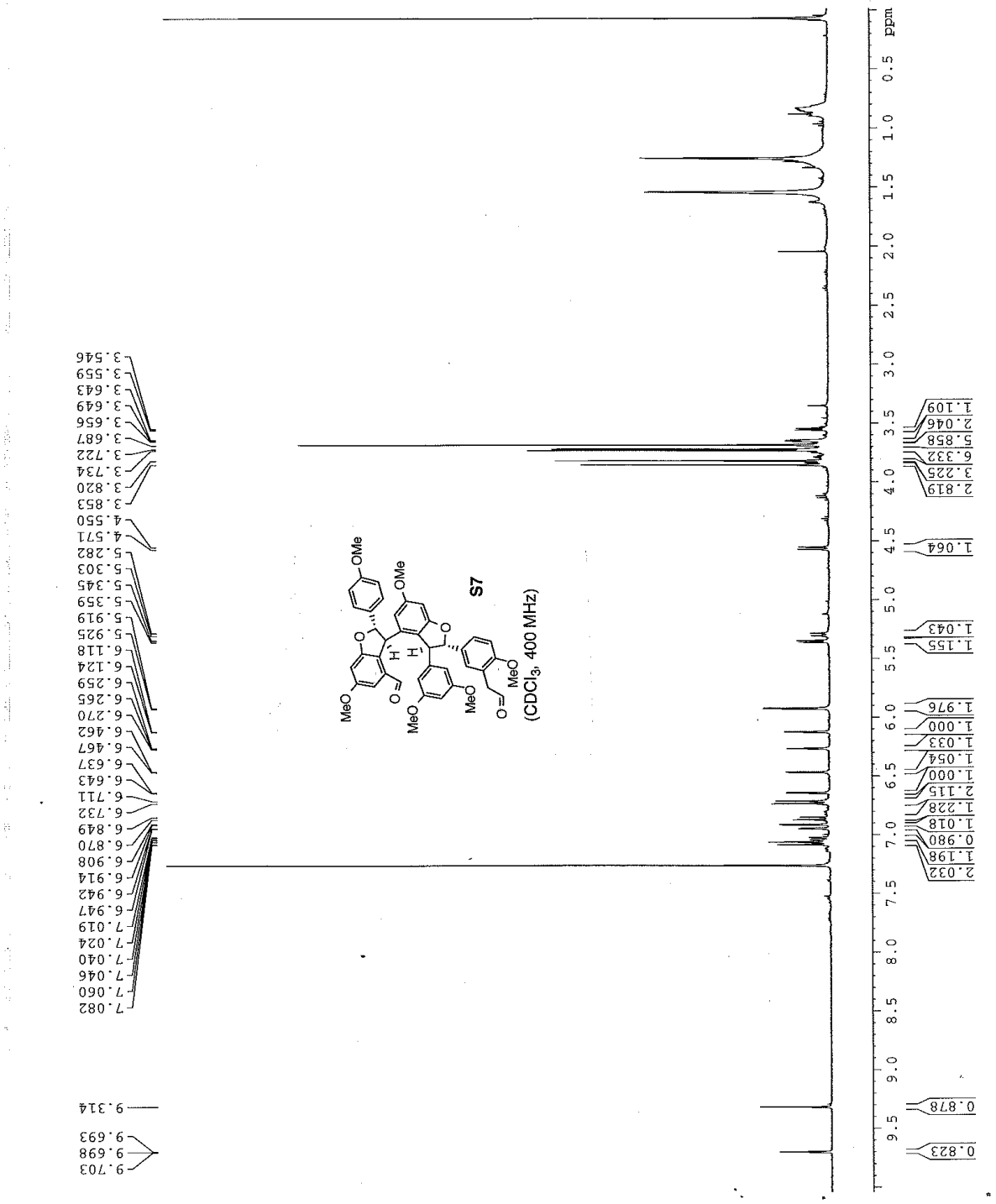
(CDCl3, 100 MHz)
ppm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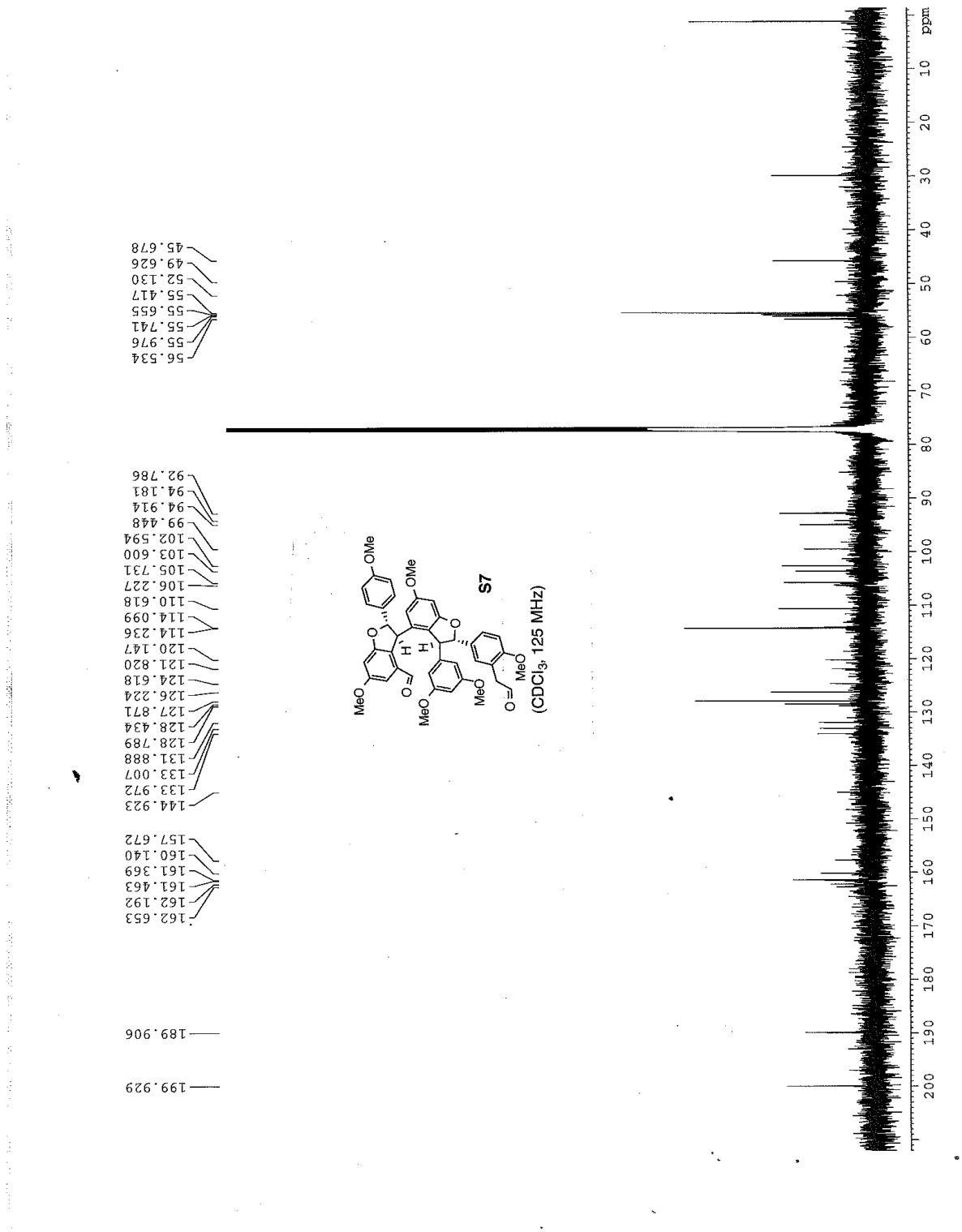
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MeO
O
O
H
H
O
O
ppm
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30
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80
90
100
110
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140
150
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170
180
190
200
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105.731
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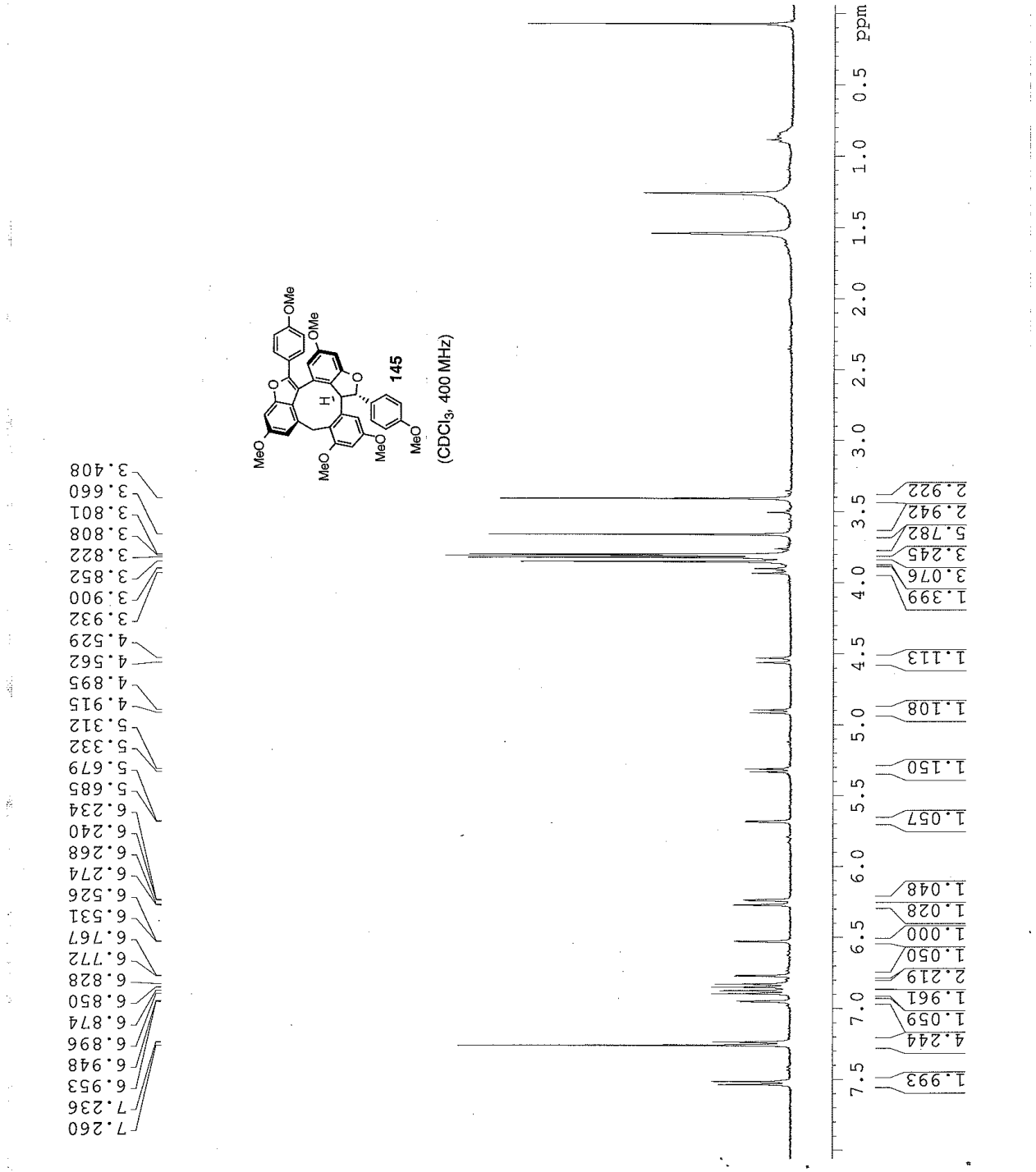
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6.850
6.828
6.772
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6.531
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6.274
6.268
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6.234
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5.332
5.312
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4.895
4.562
4.529
3.932
3.900
3.852
3.822
3.808
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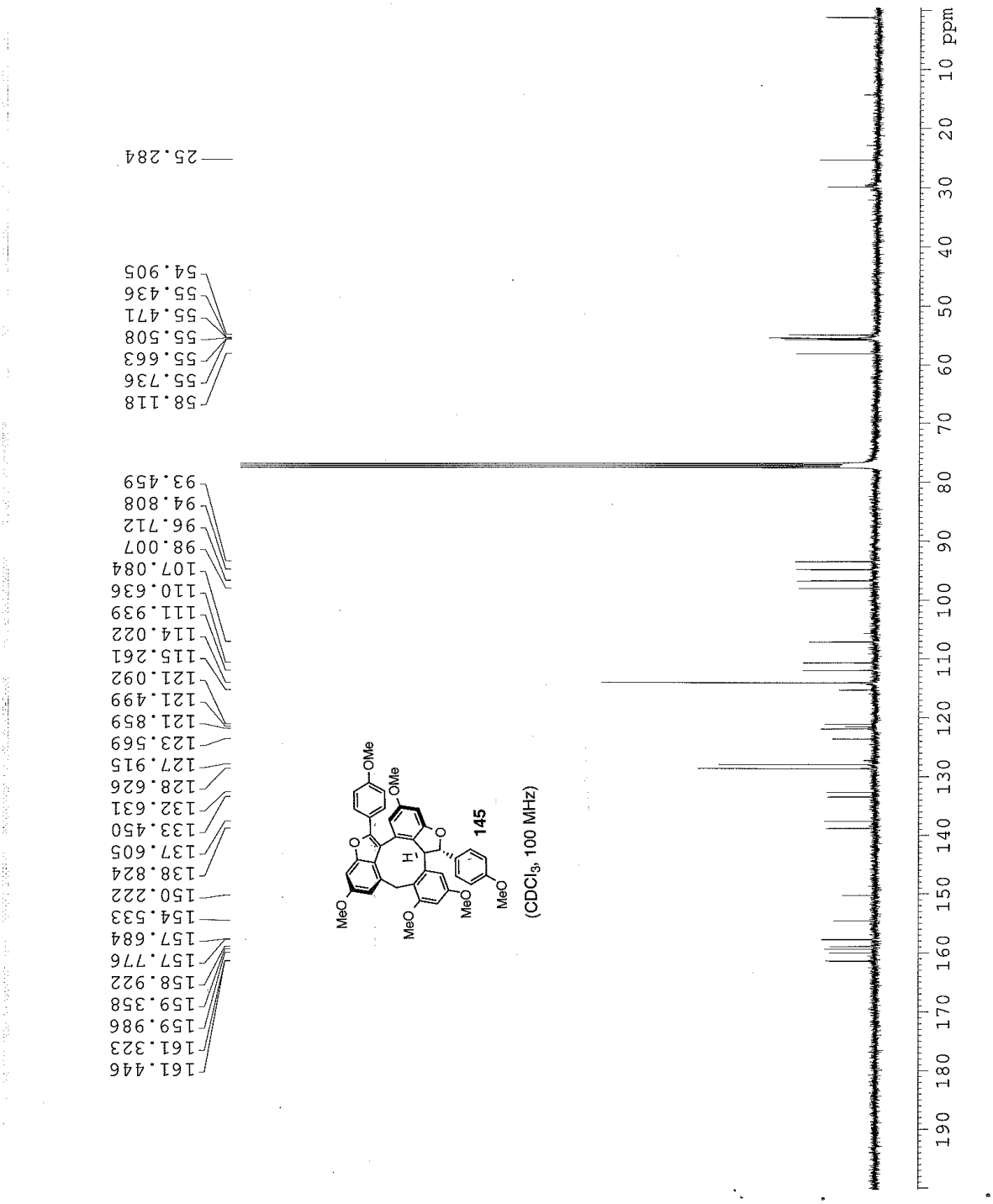
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MeO
MeO
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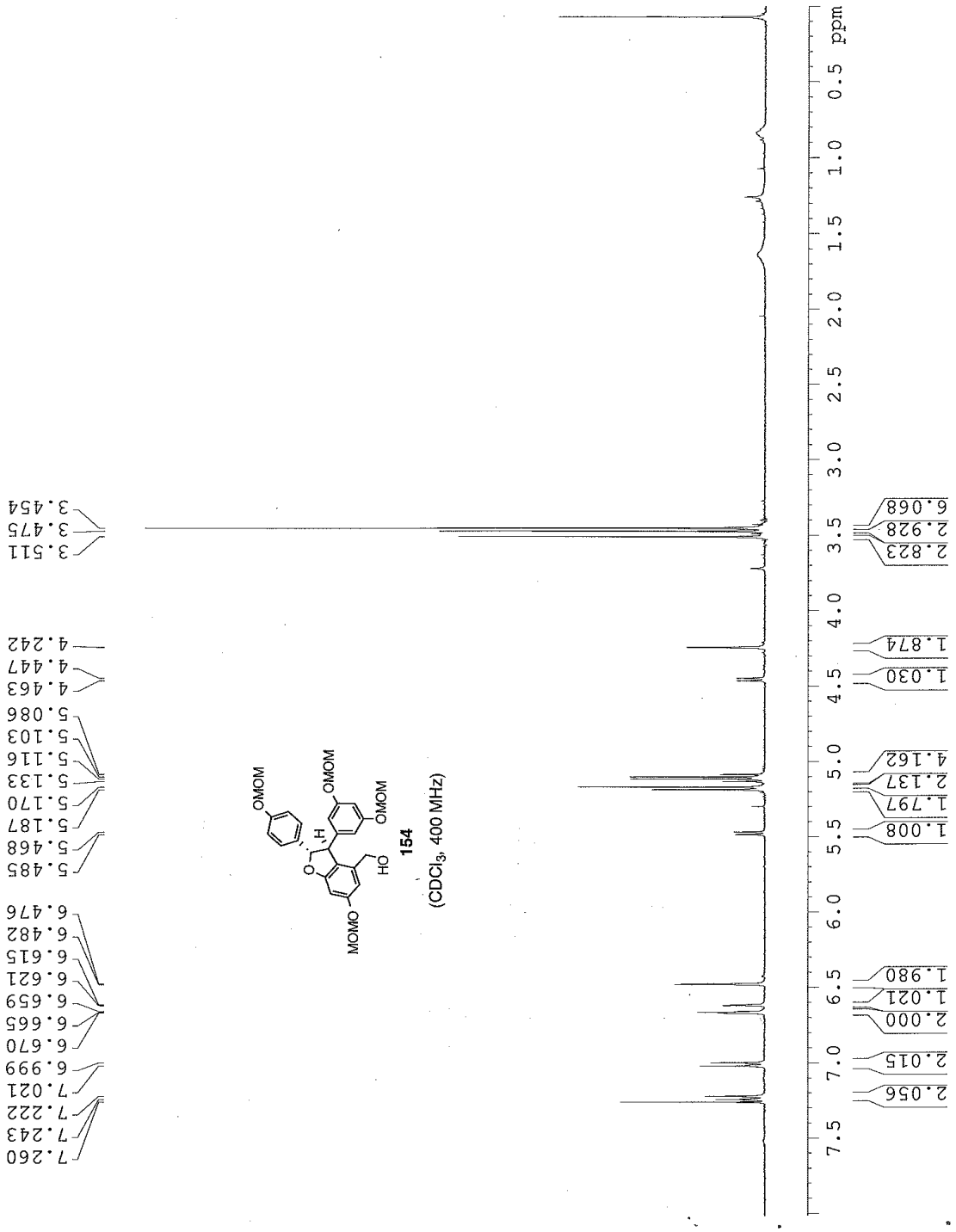
(CDCl3, 100 MHz)
10 ppm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6.621
6.615
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6.476
5.485
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5.170
5.133
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3.475
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2.0
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1.0
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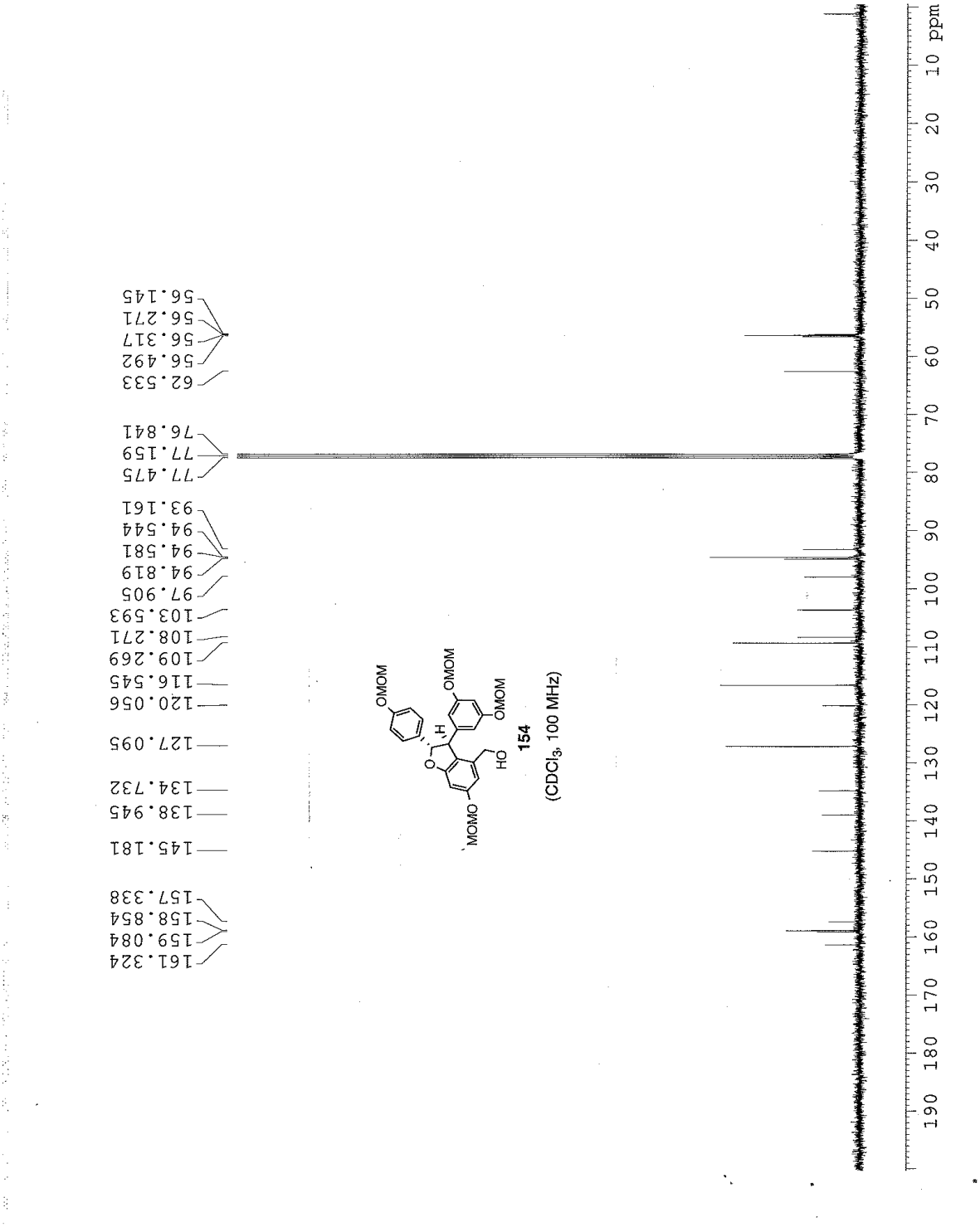
ppm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O
HO
MOMO
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138.945
134.732
127.095
120.056
116.545
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108.271
103.593
97.905
94.819
94.581
94.544
93.161
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56.317
56.271
56.145
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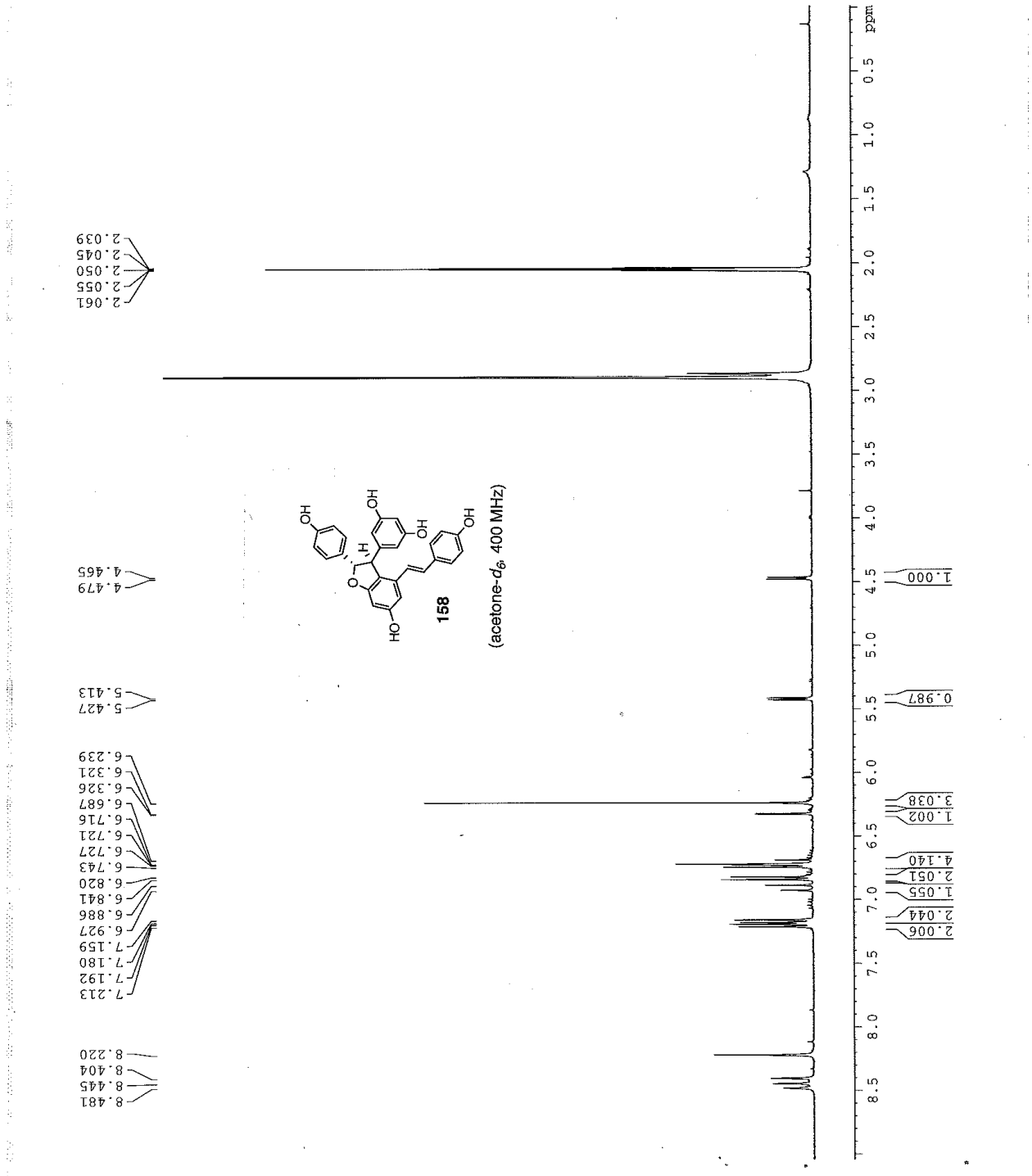
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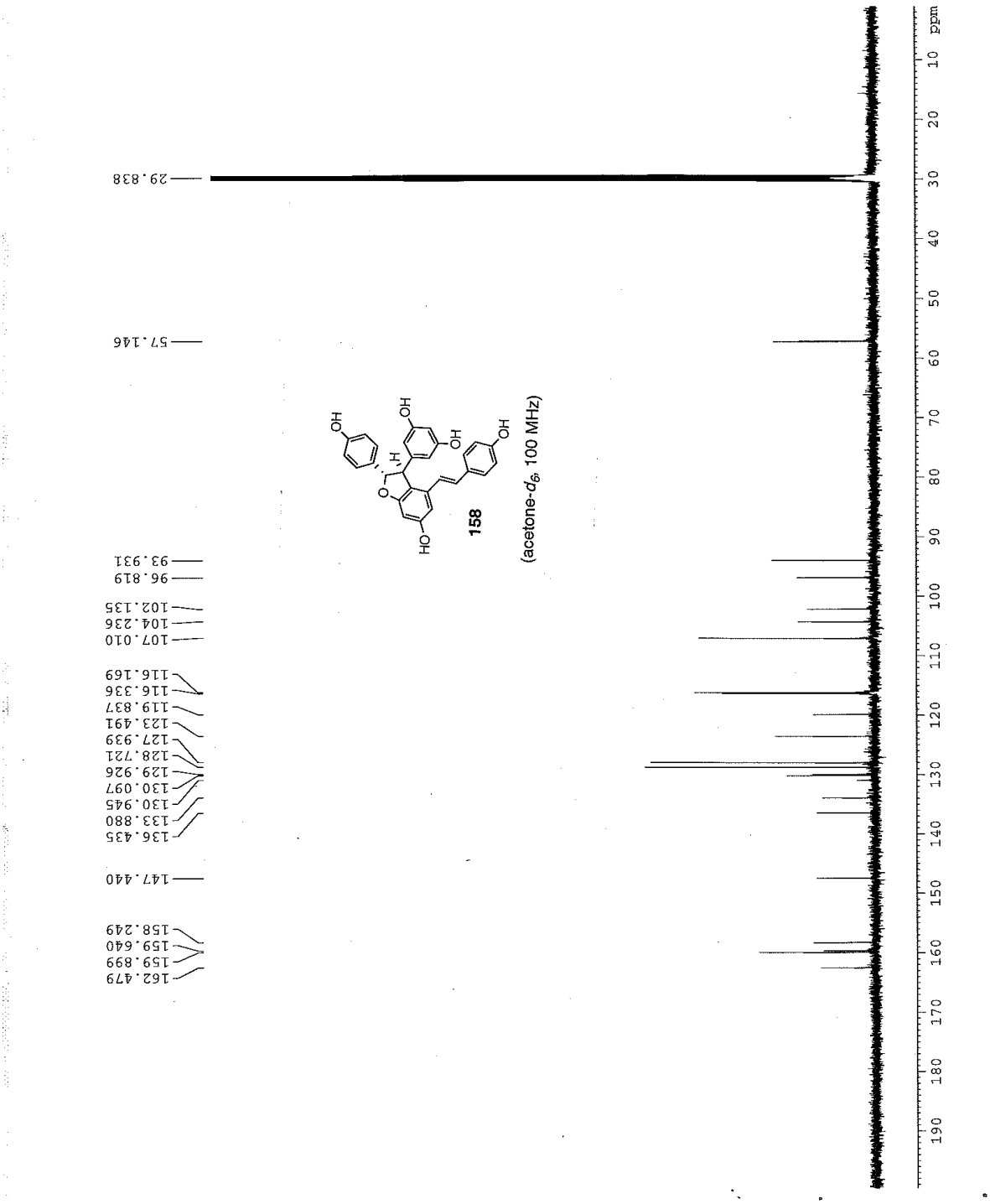
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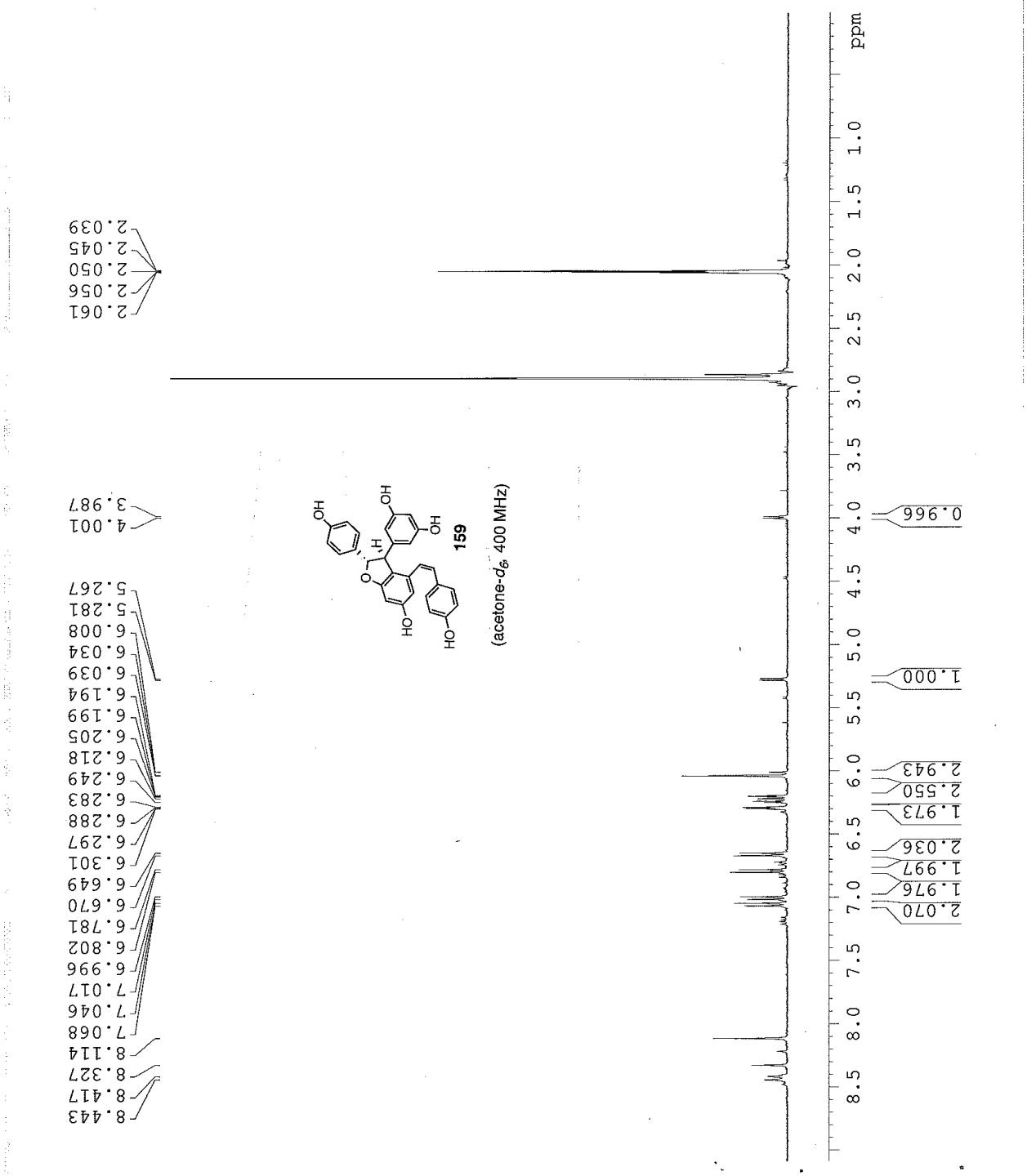
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3.5
3.0
2.5
2.0
1.5
1.0
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1.000
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2.036
1.997
1.976
2.070
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8.114
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6.199
6.194
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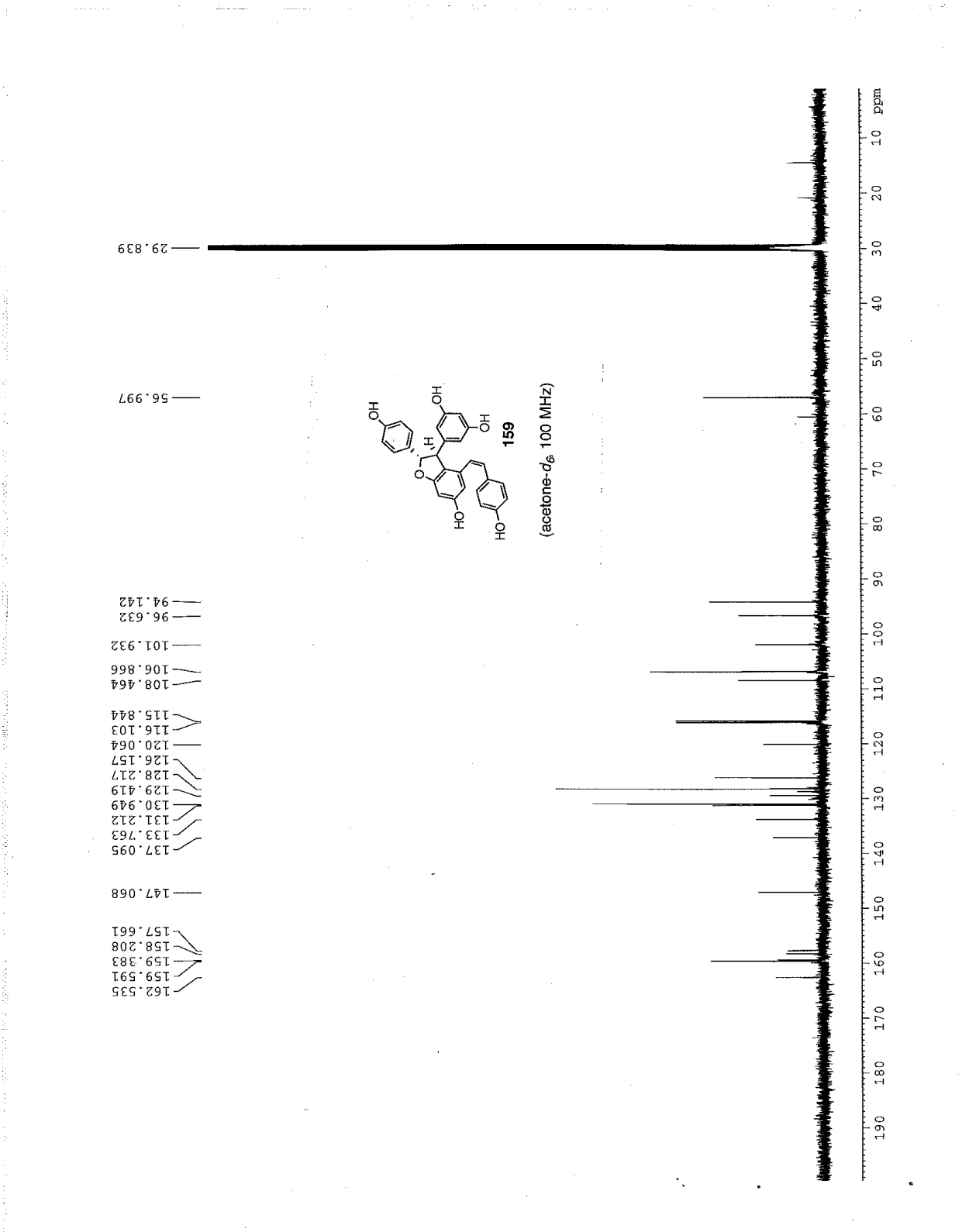
2.045
2.039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128.217
129.419
130.949
131.212
133.763
137.095
147.068
157.661
158.208
159.383
159.591
162.535
159
(acetone-d_6, 100 MHz)
ppm

Chapter 4

[1.1.1]-Orthocyclophanes and the Synthesis of the Elusive Triketone

4.1 Introduction

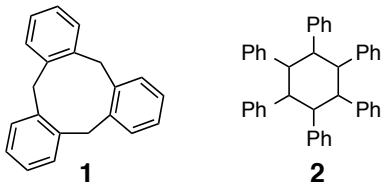
The total synthesis of natural products serves as a breeding ground for countless discoveries and innovations in the field of chemistry. Apart from the direct goal of developing a successful synthetic strategy to access a naturally derived target, it also is the job of the chemist to uncover weaknesses in the current selection of synthetic methodology and develop solutions to overcome them. Additionally, with the ever-expanding fields of materials science, polymer chemistry, and supramolecular organization, there exists a need to conquer the organic synthetic limitations revealed in those arenas that are preventing their further and more rapid expansion. In a more general, colloquial sense, the organic chemist must constantly be "on the lookout" for applications of their science to all facets of chemistry that incorporate carbon-based molecules into their operations. It is in this vein that we present our contribution to the field of supramolecular chemistry, particularly those applications which utilize [1.1.1] orthocyclophanes as host molecules (see Figure 1), distilled from our efforts toward 9-membered ring containing natural products (Chapter 3). To appreciate the value of this work fully, a brief review of this molecular class and its current applications is necessary first.

4.2 The Discovery of the [1.1.1] Orthocyclophane Series

Shown in Figure 1 are the compounds 10,15-dihydro-5*H*-tribenzo[a,d,g]cyclononene (**1**), hereafter referred to as "the parent [1.1.1] orthocyclophane," and hexaphenyl cyclohexane (**2**) with undefined stereochemistry. Intriguingly, compound **1** was synthesized 150 years prior to its correct structural assignment, with Canizzaro reporting in 1854 the formation of a cyclic hydrocarbon with the general formula $(C_7H_6)_n$ upon treatment of benzyl alcohol or dibenzyl ether with a number of Brønsted or Lewis acids.[1] Subsequent employment of this procedure by other

researchers claimed that the so-obtained compound was 1,2,3,4,5,6-hexaphenylcyclohexane (**2**),[2]

Figure 1. The Parent [1.1.1] Orthocyclophane **1** and hexaphenylcyclohexane **2**.



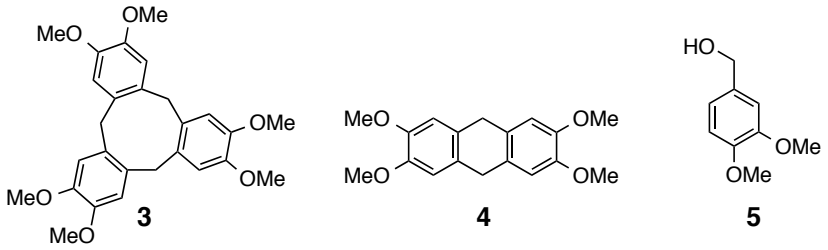
1 **2**

the product of hexamerization of the starting benzyl alcohol. These reports were largely unaccompanied by specific experimental procedure or evidence until 1941 when Shriner and Berger published an article detailing the melting point of this mystery product to be 278 - 280 ºC and the molecular weight to be loosely consistent with that of compound **2**.[3] In 2008, Grealis *et al*. synthesized and confirmed the structure of two diastereomers of the hexamer **2** using an alternate method of preparation[4] and found that the melting points of these new compounds were drastically different from that reported by Shriner and Berger. Admitting that other diastereomeric outcomes could account for the discrepancy, Grealis *et al*. sought to reproduce the unsubstantiated reports of the last 150 years concerning this mystery compound and properly determine its structure with modern analytical methods. In so doing, they obtained a small amount of a crystalline product from the acid-catalyzed oligomerization of benzyl alcohol, identical to the previously reported procedures, with a melting point of 279 ºC. In addition to NMR analysis, X-ray crystallography unambiguously determined the identity of this structure as the parent [1.1.1] orthocyclophane (**1**), thus leading the authors to report that the first synthesis of this C_{3v}-symmetric product was accomplished by Canizzaro in 1854. It has since been synthesized more efficiently by other methods, to be discussed in Section 4.3.

Cyclotriveratrylene (**3**) has a similarly mis-assigned history. In 1915, Gertrude M. Robinson, wife of the renowned Nobel laureate Sir Robert Robinson of Robinson annulation fame, reported that upon treatment with H_2SO_4 and AcOH, veratryl alcohol (**5**), produced a

symmetric oligomer which was assigned as the dimeric, dihydroanthracene product **4**.[5] The yield

Figure 2. Cyclotriveratrylene and Related Structures.



of this material is reported as nearly quantitative by the employment of 60% H_2SO_4 with veratrole and formaldehyde. Not until 1965 was it revealed by Lindsay that the product of this reported condensation was in fact the trimer (**3**), and not the dimer (**4**), so determined by accurate molecular weight measurements and careful analysis of previously misinterpreted data.[6] Since this conclusive report of the structure of cyclotriveratrylene in 1965, interest in the compound has grown enormously, and the list of various applications for this class of molecules continues to expand. We will review the synthetic approaches and derivatizations of [1.1.1] orthocyclophanes as a class and follow then with a thorough survey of their applications.

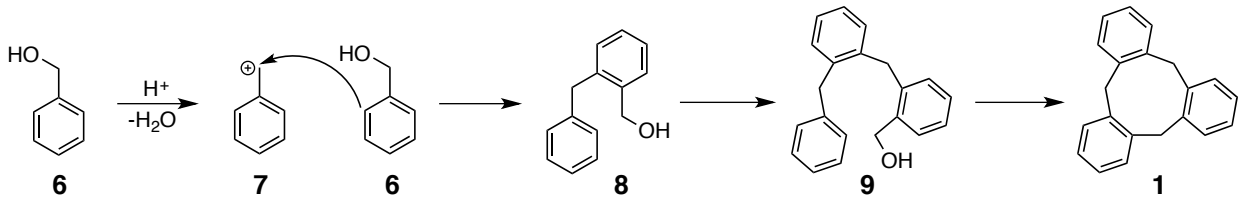
4.3 Synthesis of [1.1.1] Orthocyclophane-Based Molecules

This exciting group of molecules has been taken in numerous directions since their intentional synthesis. As such, a purely chronological review of their syntheses would be highly convoluted in terms of alternate structural features. The survey provided in the context of this thesis will be divided into the following five categories for a more coherent presentation and general level of understanding: symmetric [1.1.1] orthocyclophanes, non-symmetric [1.1.1] orthocyclophanes, chirality, methylene oxidation, and alternative orthocyclophane-like molecules. For substrates with multiple methods of construction, only the first and the most successful synthetic strategies will be presented.

4.3.1 Synthesis of C_{3v} Symmetric [1.1.1]-Orthocyclophanes

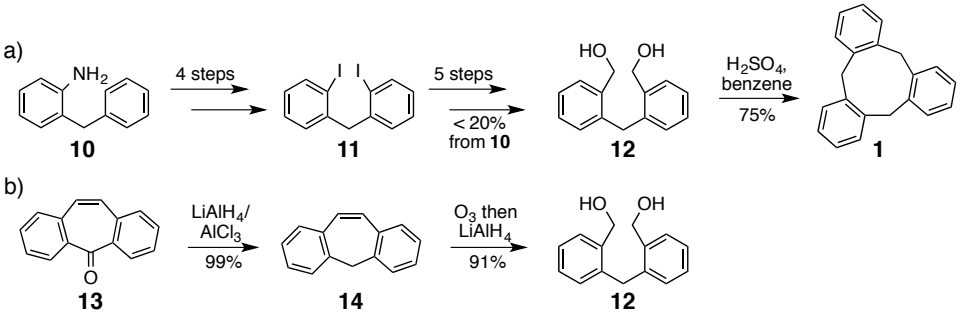
The first synthesis of the parent compound was accomplished, albeit unknowingly, 160 years ago by treatment of benzyl alcohol with various Lewis and Brønsted acids (Section 4.2). As has been noted in subsequent publication of this and similar strategies, the yield is very low. Absent the electron-donating assistance of *para*-disposed electron donating groups (examples to be shown hereafter), generation of the benzylic cation **7** as shown in Scheme 1 appears to be

Scheme 1. Acid-Catalyzed Oligomerization of Benzyl Alcohol



prohibitively unfavorable for significant conversion. This effect is amplified, as the event must occur three a total of three times (including the cations derived from alcohols **8** and **9**). As a result, alternate and very versatile synthetic methods have been sought and developed. Shown in Scheme 2a is a summary of the first intentional synthesis of orthocyclophane **1** by Sato and Uno.[7] While the final product-forming step occurs in a good yield of 75%, as do many of the early steps, the sequence is quite lengthy to achieve requisite precursor **12**. Finding this original

Scheme 2. a) Synthesis of **1** by Sato and Uno in 1977; b) Synthesis of Diol **12** by Schmuck and Wienand

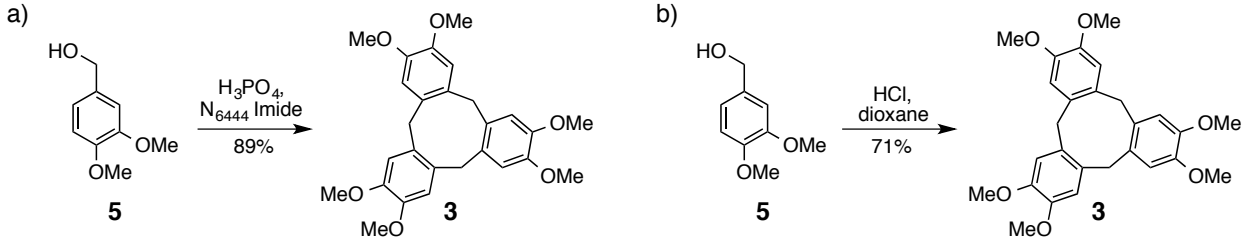


synthesis to be overly tedious toward the diol intermediate **12**, Schmuck and Wienand sought an alternate approach.[8] Ultimately, they devised starting point **13**, the cheap and commercially

available dibenzosuberenone, and developed the more straightforward and reliable method outlined in Scheme 2b. Here, ketone reduction with $LiAlH_4$ proceeded very smoothly to give dibenzosuberene **14**, after which ozonolysis and reduction furnished the 9-membered ring precursor **12**. At this point, the original work by Sato *et al*. was adopted, with H_2SO_4-catalyzed ring formation. Together this route accomplishes the most efficient synthesis of the parent [1.1.1] orthocyclophane in terms of length and overall yield.

Regarding substituted, C_{3v}-symmetric [1.1.1]-orthocyclophanes, there are many in existence with the most prevalent being cyclotriveratrylene (**2**). As mentioned in Section 4.2, the original synthesis of this compound was achieved in 1915 with the correct structural assignment following fifty years later in 1965. Since then, a number of syntheses have taken place, with two of the most efficient shown in Scheme 3. The highest yield is achieved using catalytic H_3PO_4 in an ionic liquid, abbreviated N_{6444} Imide.[9] This procedure holds value both in terms of yield

Scheme 3. Synthesis of Cyclotriveratrylene in a) an Ionic Liquid; b) Conventional Organic Solvent.

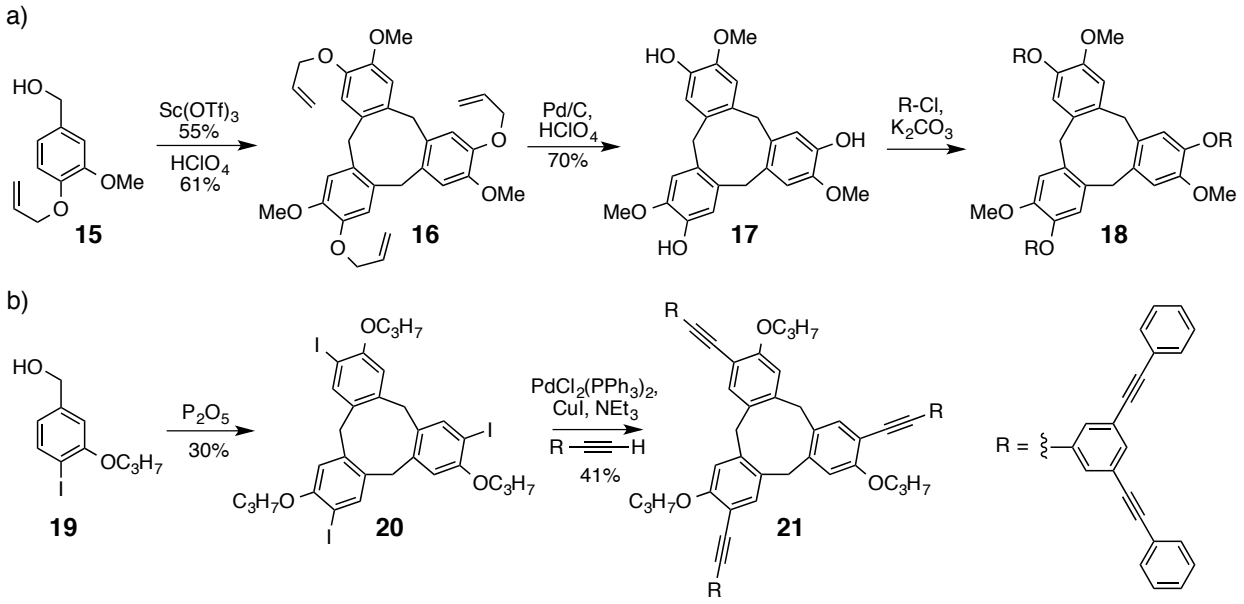


(up to 89%, the highest reported) as well as minimizing waste and harmful bi-products. In a more conventional approach, treatment of the same veratryl alcohol **5** with HCl in 1,4-dioxane delivered the desired product in 71% yield after five hours of reaction time.[10] This method has been used to generate other derivatives in a single step with varying patterns of oxygen substitution.

Of particular interest has been the ability to derivatize these structures from the outer rim (the aromatic rings), thereby allowing for the installation of numerous other functional groups.

Perhaps the most useful intermediate for such endeavors is the product of cyclic trimerization using partially allylated precursor **16**. As shown in Scheme 4, this intermediate has been successfully produced using the $Sc(OTf)_3$-catalyzed conditions described by Brotin *et al*.[11], or

Scheme 4. Elaboration of Cyclotriveratrylene Analogues Via a) Etherification; b) Pd Cross-Coupling.

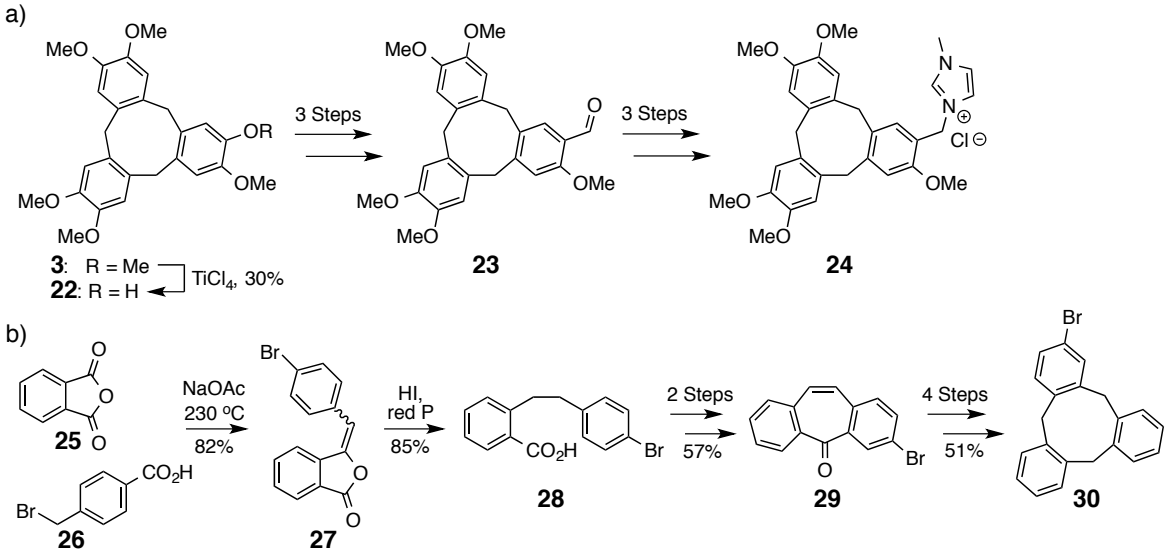


using $HClO_4$, which allowed for access to this key springboard compound in a reasonable yield from the monomeric precursor **15**.[12] Moving forward from **16**, the allyl groups are then removed to give **17,** revealing only three free phenols, which could then be elaborated via etherification or esterification to give structures generically characterized by compound **18**.[12,13] Direct formation of the tri-iodo compound **20** has been accomplished by P_2O_5 treatment of alcohol **19** with subsequent demonstration of its potential towards cross-coupling using the Sonogashira reaction to yield products like **21** with interesting photophysical properties.[14] While the compounds presented thus far fairly represent the category of C_{3v} symmetry in this class of molecules, there is also a potential need to manipulate a single position, a goal which would require preparation of a non-C_{3v} symmetric analogue.

4.3.2 Synthesis of Non-C_{3v} Symmetric [1.1.1]-Orthocyclophanes

While there has been great interest in the synthesis of [1.1.1]-orthocyclophanes where one of the rings differs from the others, the state of the art solutions for producing such structures have significant limitations both in yield and overall efficiency. Select examples are shown in Scheme 5 to illustrate this point. One instance is found in the preparation of cyclotriveratrylene monophenol (**22**) through selective deprotection of its permethylated variant (**3**); this operation, unsurprisingly, was only achieved in 30% yield with various other degrees of demethylation generally observed in the process.[15]

Scheme 5. Synthesis of Non-Symmetric [1.1.1] Orthocyclophanes.



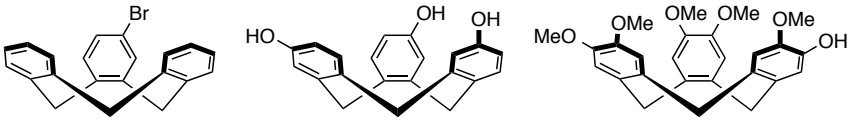
Once in hand, this lone phenol has been replaced with a carboxaldehyde moiety to give **23**, a compound which readily undergoes standard transformations as shown in Scheme 5a to give NHC catalyst **24**. This compound has been subsequently used for the Michael addition of oxygen nucleophiles. A second example shown in Scheme 5b displays the successful synthesis of monobrominated compound **30**, though it requires a somewhat lengthy preparation including several instances of extremely high reaction temperatures.[8] Again, once achieved, that functional handle is equipped to access numerous analogues. Other attempts to achieve mono-manipulation

of these structures through single C-H functionalization of a C_{3v} symmetric precursors were likewise plagued with issues of selectivity towards the mono-adduct.[16] A clear deficiency is present in terms of a general strategy to vary a single aromatic ring.

4.3.3 Chirality Among [1.1.1] Orthocyclophanes

When the aromatic rings of any [1.1.1] orthocyclophane are not symmetrically substituted, an axis of chirality is created. Due to the energy barrier of a "ring-flip" of the central nine membered ring being relatively high for molecules of this type, these enantiomers can often be separated and manipulated as distinct chiral entities; the examples shown in Figure 3 are rendered three dimensionally so as to better display this chiral character. While separation via chiral HPLC was achieved in the case of brominated compound **30**,[8] [1.1.1]-orthocyclophanes **31**

Figure 3. Chiral [1.1.1] Orthocyclophanes That Have Been Resolved Into Their Respective Enantiomers.



30 **31** **22**

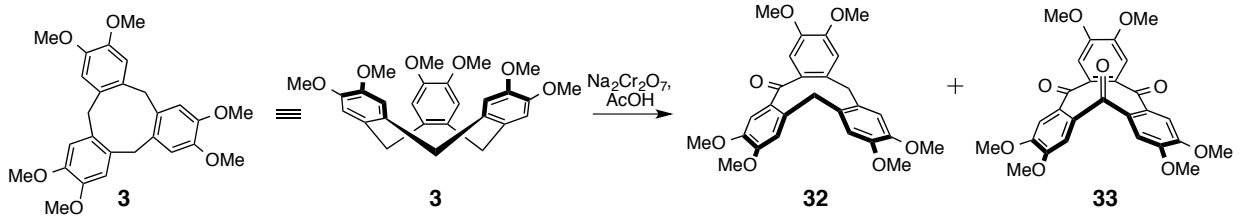
and **22** required the appendage of an enantiomerically pure auxiliary (2-phenoxypropionic acid for **31** and camphor in the case of **22**) after which separation was accomplished and structures confirmed by measurement of optical rotation.[15b,17] The example shown for compound **22** was published in 2013, where the authors note that these breakthroughs lay the foundation for future research based on optically pure variants of these molecules, indicating that this achievement is relatively recent and applications for such scaffolds are anticipated in the future.

4.3.4 Benzylic Oxidation and Conformation of [1.1.1] Orthocyclophanes

While elaboration of the outer rim of this class of molecules has opened the door to

numerous substrates and applications, little has been done with the methylene positions between the aromatic rings, also known as the "inner rim." The first foray into this line of reactivity was reported in 1968 by Cookson and co-workers when they treated cyclotriveratrylene (**3**) with $Na_2Cr_2O_7$ in AcOH. The isolation of monoketone **32** was reported as well as a small amount of the triketone (**33**) with the comment that more triketone can be obtained upon resubmission of the monoketone to the reaction conditions as shown in Scheme 6.[18] They then proceed to

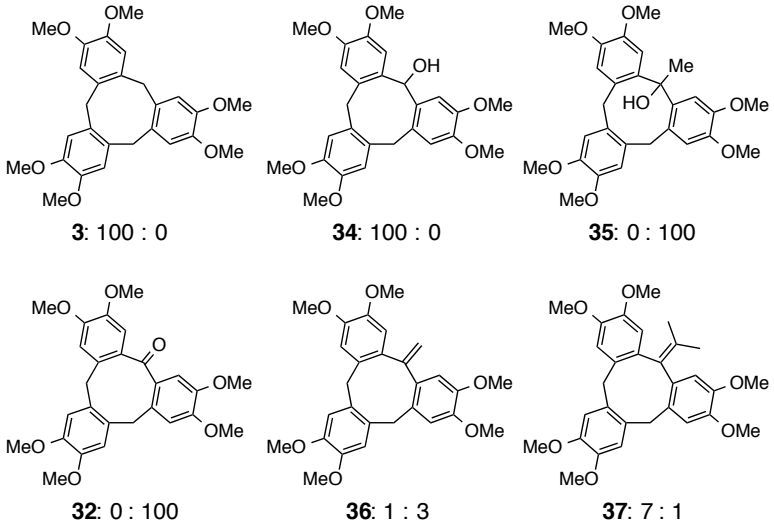
Scheme 6. Oxidation of Cyclotriveratrylene



describe, in detail, the likely conformations adopted by these structures, particularly the "crown" conformation and the "saddle" conformation. The starting material **3** is widely accepted to occupy a crown conformation because there are only two ^{1}H-NMR peaks for the methylene hydrogens showing that each methylene is equivalent, but the geminal hydrogen atoms have distinct relationships with the rest of the molecule. These methylene NMR signals did not coalesce even at temperatures up to 200 ^oC indicating a high energy barrier for conformational conversion; this barrier was later determined to be 26.5 kcal/mol by racemization of a labeled, chiral variant.[19] Were the monoketone **32** to occupy a similar crown conformation, however, the π-orbitals of the carbonyl group would fail to benefit from conjugation with those of the neighboring aromatic rings; in fact, they would be orthogonal. This notion, along with the observation that the remaining two methylene groups with four total aliphatic hydrogens, exhibit only a singlet all the way down to -60 ^oC in the ^{1}H NMR spectra, indicate that the monoketone inhabits a "saddle" conformation. Furthermore, the authors note that, "this result is that expected

only if molecular inversion of a "saddle" conformation (and consequent averaging of the environments of the methylene protons) is rapid at all temperatures investigated." Other derivatives of the mono-ketone have been generated and are shown in Figure 4 with the observed ratios between the crown and saddle conformations indicated below the structures. The main conclusion that the authors drew is that with tetrahedral geometry about the aliphatic positions (**3**, **34**-**35**), the crown conformation is preferred, however, in the case of tertiary alcohol **35** the two substituents prevent conformational flip from the more flexible saddle conformation to the

Figure 4. Various Cyclotriveratrylene Derivatives With Their Observed Conformational Ratios (Crown : Saddle).

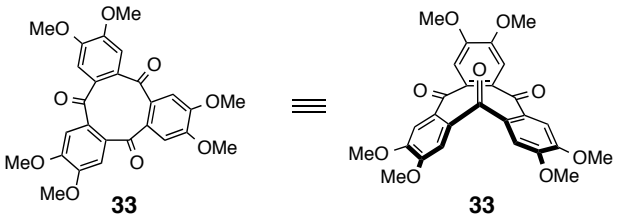


crown, thus making the saddle the observed form. When one of the aliphatic positions is trigonal (**32**, **36**-**37**), the benefit of conjugation with the aromatic rings causes the preference to now lean towards the saddle conformation since it allows for such stabilization. In the case of isopropylidene **37**, this electronic benefit is outweighed by an unfavorable steric interaction between the geminal dimethyl group and the *ortho*-disposed aromatic hydrogen.

As mentioned, in addition to the monoketone, which was obtained in 43% yield from chromic acid oxidation of cyclotriveratrylene **3**, a 5.4% yield of the triketone **33** was also reported (Figure 5). Cookson *et al.* assigned this structure based on the disappearance of six

hydrogen signals from the ^{1}H NMR of **3** and the appearance of three oxygen atoms in its mass spectrum due to an increase in molecular weight by ~ 42. Two carbonyl stretches (1750 cm^{-1} and 1598 cm^{-1}) are also observed in the IR. This finding led them to the conclusion that the triketone **33** adopts a saddle conformation wherein two of the carbonyl groups are able to obtain

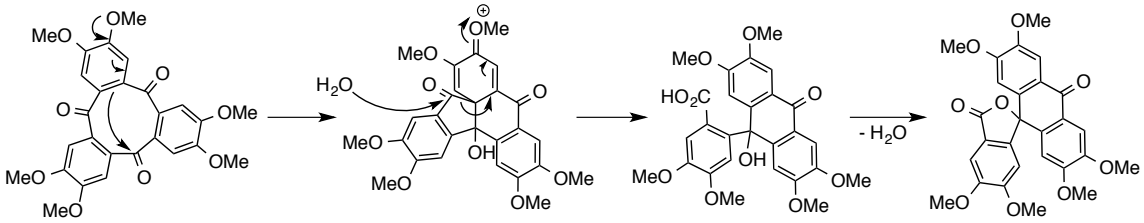
Figure 5. Triketone Reported From Cyclotriveratrylene Oxidation



orbital alignment with a neighboring aromatic ring, both accounting for the 1598 cm^{-1} stretch, while the third is held out of conjugation with the aromatic systems giving it the 1750 cm^{-1} stretch. Additionally, it is concluded that the conformation is rigid with no equilibration as indicated by the six distinct methyl groups and six distinct aromatic proton signals in the ^{1}H NMR spectra. Lastly, the authors conclude that despite an inability to convert this triketone back into cyclotriveratrylene **3** via reduction, the "lack of fragmentation in the mass spectrum" indicates that the 9-membered ring skeleton of **3** is intact.

Later that same year (1968) a report by Baldwin and Kelly definitively refutes the claim that the obtained "triketone" **33** from Cookson is in fact a triketone.[20] Rather, they argue it possessed the spirocyclic lactone structure of **40**, one resulting from the transannular rearrangement shown mechanistically in Scheme 7. The authors of this publication draw on the known spectral data of highly related anthrone structures as well as the ability to convert such structures into the lactone **40** obtained by this oxidation.

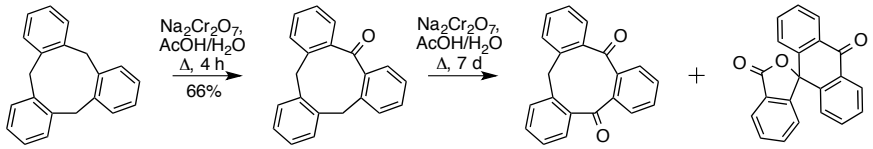
Scheme 7. Proposed Rearrangment of Triketone **33**.



33 **38** **39** **40**

Similar results were obtained when the analogous reactions were performed on the parent [1.1.1]-orthocyclophane **1** as shown in Scheme 8.[16] In this case, monoketone **41** was obtained in a 66% yield through chromic acid oxidation. Further exposure of **41** to the reaction conditions gave 25% of diketone **42** as well as 11% of lactone **43**, with the triketone assumed as an intermediate in its generation. In this report, Yamato and Sakaue are able to observe resolution

Scheme 8. Oxidation of the PArent [1.1.1] Orthocyclophane **1**.



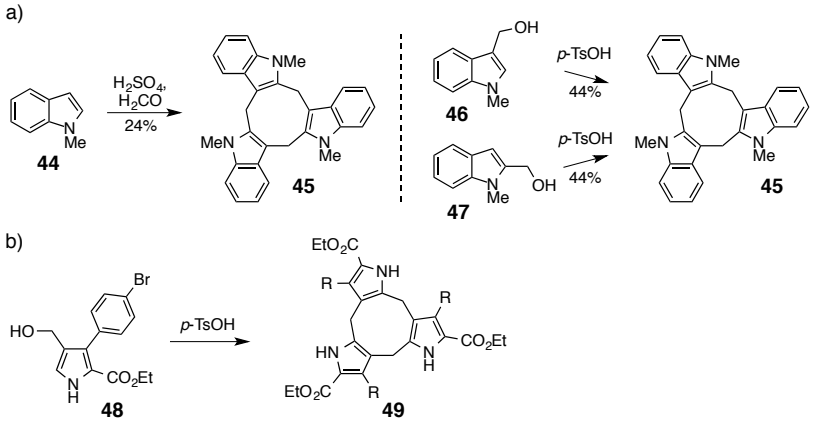
1 **41** **42**: 25% **43**: 11%

of the methylene protons in both the mono- and di-ketone structures at -110 ^{o}C and -115 ^{o}C, respectively, indicating slightly more flexibility in the diketone structure. While other reports of [1.1.1]-orthocyclophane oxidation have since been published by other investigators, they either confirm or simply cite these two works regarding any attempt to isolate triketone **33**. Further elaboration of the mono- or di-ketones has not been reported apart from the minor manipulations by Cookson *et al*. performed solely for the purposes of conformational investigation. Were the elusive **33** to be obtained, symmetric elaboration from the inner rim would be enabled, thus opening an entirely new mode of manipulation of potential benefit to the numerous applications currently being explored with these molecules.

4.3.5 Development of [1.1.1] Orthocyclophane-Like Molecules

Before we begin a discussion of the practical application of this class of structures, we will briefly present a number of highly related structures to the above-described molecules and the manner in which their synthesis was achieved. The first indole variant of a [1.1.1]-orthocyclophane **45** was reported in 1970 by Bergman and co-workers from the acid-catalyzed condensation of 1-Me-indole (**44**) and formaldehyde, a process which occurred in 24% yield as shown in Scheme 9a.[21] These researchers note that the existence of a singlet in the ^{1}H NMR spectra for the methylene protons as opposed to the well-resolved doublets observed for cyclotriveratrylene **3**, indicating that **45** is likely in the rapidly equilibrating saddle conformations and not a crown conformation. Nearly 40 years later, Santoso *et al.* supported this conformational claim with an X-ray crystal structure showing **45** to be in a saddle conformation.[22] This team also synthesized a number of analogues varying in both nitrogen protecting group and aromatic substitution (with yields generally between 44-48%) by treatment of 2- or 3-hydroxymethyl indole derivatives, such as **46** and **47**, with *p*-TsOH in CH_2Cl_2; interestingly, submission of both regioisomers produced equivalent results. In the absence of *N*-

Scheme 9. Synthesis of [1.1.1] Orthocyclophanes with a) Indole and b) Pyrrole.

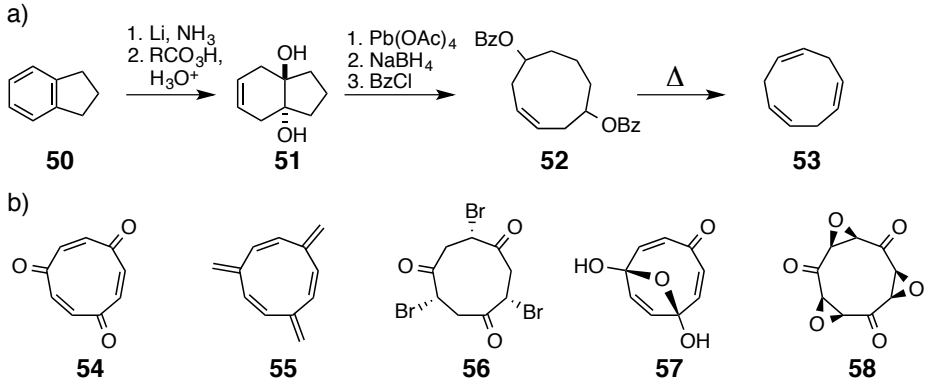


methylation, compound **45** exhibits high affinity for the estrogen receptor signaling pathways and is under investigation as a potential cancer therapy.[23] In a similar vein, a pyrrole version of a

[1.1.1]-orthocyclophane was first synthesized in 1970 with other reports coming later.[24] Earlier syntheses suffered from poor yields and selectivity, but in 2000, through the strategy outlined in Scheme 9b, Fumoto *et al.* devised a more efficient synthesis of these compounds from highly functionalized pyrrole precursors like **48**.[25] Unlike the indole compound **45**, **49** adopts a rigid crown conformation much like cyclotriveratrylene itself, albeit with a smaller energy barrier to inversion (one determined to be 15 kcal/mol).

In our final category of cyclotriveratrylene-like molecules, the fused aromatic rings are replaced by simple, disubstituted *Z*-alkenes. The unelaborated parent compound was first reported in 1963 by the synthesis outlined in Scheme 10a, beginning from indane **50** through cleavage of the transannular bond in **51** to give elimination precursor **52**.[26] NMR measurements revealed this compound to inhabit a crown conformation although inversion appears to be operative with a far smaller energy barrier than with those compounds discussed above. Much later, in 1995 and again in 2007, the Prinzbach group detailed their efforts to obtain the compound *cis,cis,cis*-cyclonona-2,5,8-triene-1,4,7-trione (**54**) shown in Scheme 10b.[27] Unfortunately, due to the transannular bond formations and intermolecular reactivity that so often plagues medium-sized ring formation and manipulation, they were unable to isolate the desired triketone **54**, only obtaining the closely related structures **55** - **58** through their synthetic

Scheme 10. a) First Synthesis of 1,4,7-cyclononatriene **53** and b) Compounds Related to Triketone **54**.



efforts. Thus, despite many efforts and reports toward the synthesis of [1.1.1]-orthocyclophanes, or orthocyclophane-like, triketone structures, none have ever been successfully produced or characterized thus far.

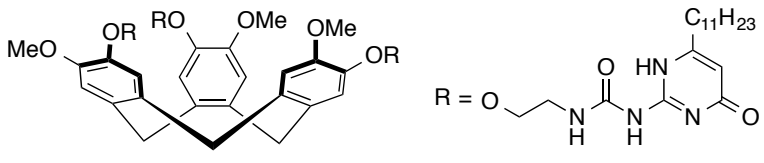
4.4 Applications of [1.1.1]-Orthocyclophanes

The applications of this class of molecules can be generally divided into two categories, those that employ a single unit of the orthocyclophane operating alone, and those that create a tribridged dimer of two orthocyclophane units called a cryptophane (see Figure 8). Examples utilizing single units will first be addressed[28] followed by a select, representative example employing a cryptophane molecule.

4.4.1 Cyclotriveratrylene-Based Hosts for Fullerenes

Owing to its rigid crown conformation, cyclotriveratrylene (**3**) creates a hollow bowl shape capable of hosting various guest molecules, among them fullerenes.[29] This property serves many useful functions, chief among them being the ability to separate mixtures of fullerenes containing $C_{60,}$ C_{70}, and C_{84} due to variable binding affinities.[30] Often success in this arena is increased through the use of "extended-cavity" cyclotriveratrylene molecules where the outer rim has been expanded such as compound **59** shown in Figure 6 with its appended 4-ureidopyrimidinone side-arms that self-assemble into a dimeric structure through complimentary

Figure 6. Extended Cavity Cyclotriveratrylene For Fullerene Hosting



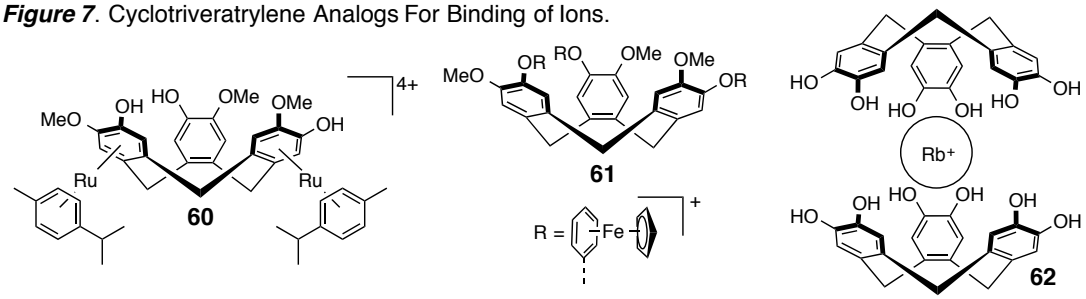
59

hydrogen bonds.[30] The resulting cavity has selective affinity for higher order fullerenes (C_{70} and C_{84}), and depending on the ratio of the fullerene mixture to **59**, each can be selected preferentially. The complexed fullerenes exhibit greater solubility and thus can be separated, after which the introduction of a more polar solvent, such as tetrahydrofuran, disengages the supramolecular complex causing precipitation of the fullerene with **59** still in solution. Similar protocols have been developed for the selective isolation of C_{60} with calixarene-type scaffolds. As the applications for, and properties of, fullerenes continue to increase in both volume and interest, methods for purifying, solubilizing, and generally hosting them will no doubt follow.

4.4.2 Cyclotriveratrylene-Based Selective Binding of Ions

Owing to their varying size and solvation effects, the selective binding of anions represents a significant challenge in host-guest chemistry. By complexing metals to the aromatic rings of cyclotriveratrylene analogues, as in **60** and **61** (Figure 7), selective binding to anions such as TcO_4^- is achieved with 95% of this particular anion being extracted from a saline solution

Figure 7. Cyclotriveratrylene Analogs For Binding of Ions.



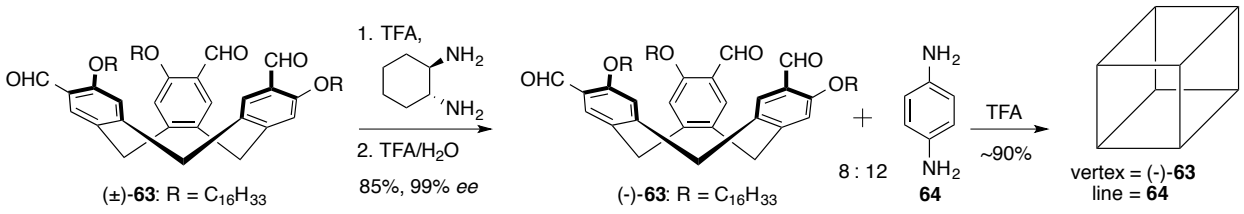
containing various ions using analogue **61**.[31] Considering that ^{99}Tc is a significant and radioactive component of nuclear waste, its selective removal is of great value.[32] In other instances, the binding capacity of particular analogues in this class is used to sense the presence and concentration of certain anions such as $H_2PO_4^-$ and ATP^-.[33] In the arena of cations, deprotonation of cyclotricatecholines (**62**) form "clam-like" dimeric structures which, even in an

aqueous environment, can selectively sequester Rb^+ or Cs^+.[34] These cations apparently prefer the aromatic environment with its soft donating capacity over that of the oxygen atoms of **62** or even those of water. As the need to selectively isolate, detect, and measure ions in various environments is present in numerous circumstances, the search for materials capable of such tasks likewise continues with [1.1.1]-orthocyclophanes showing exciting proficiency and potential.

4.4.3 Cyclotriveratrylene-Based Self-Assembled Nanostructures

The successful generation of nanoscale capsules opens up possibilities in purification science, as described above, as well as guest encapsulation and delivery to certain targets. Use of these structures as potential nanoreactors has also been proposed. An exciting example in this field was recently contributed by Xu and Warmuth as they not only employed a dynamic thermodynamic resolution to obtain an enantiopure sample of a cyclotriveratrylene analogue **63**, but they also induced self assembly of eight of these units to generate a "nanocube" cavity.[35] Their strategy is detailed below in Scheme 11. Condensation of the starting trialdehyde **63** with (*R,R*)-diaminocyclohexane at 80 ºC, wherein one enantiomer of **63** condenses while the other inverts before condensing, thus producing the product cryptophane (not shown) in 99% *ee*. This

Scheme 11. Synthesis of a Homochiral Nanocube



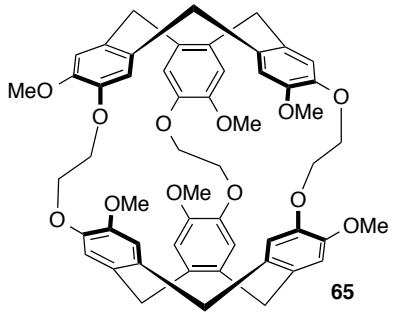
material is then hydrolyzed to furnish the now enantioenriched starting material (-)-**63** which, upon mixing with 1,4-diaminobenzene **64** gives a 90% yield of the chirally pure nanocube with the eight vertices consisting of eight units of (-)-**63** and diamine units **64** having condensed onto

the aldehydes to create diimine bridges. The authors close their report with the forward facing proposition, "our cubes have dimensions that approach those of small globular proteins and may in fact be able to serve as alternative vessels for biomacromolecules." With ever expanding applications being uncovered for [1.1.1]-orthocyclophanes the need for control and variety in their synthesis likewise increases.

4.4.4 Cryptophanes as Hosts For Xenon

While cryptophanes possess many of the same abilities described above for [1.1.1]-orthocyclophanes on their own,[36] those will not be addressed and our discussion will focus on one particularly noteworthy application: the encapsulation of xenon. Seeing as cryptophanes are simply the covalently linked dimers of [1.1.1]-orthocyclophanes, a discussion of their use is appropriate for this work. Of late, xenon-129 has emerged as a very attractive contrasting agent for MRI as compared to more conventional agents due to its strong signal and very wide shift window that allows for sensitivity to even minute environmental changes.[37] With these highly desirable properties, there is a great need for methods that couple ^{129}Xe magnetic resonance to biomarkers of interest. Cryptophane **65,** shown in Figure 8, has demonstrated the ability bind ^{129}Xe with high affinity.[38] Wei *et al*. in a 2006 report have utilized the affinity of **65** for ^{129}Xe and

Figure 8. Cryptophane **65**

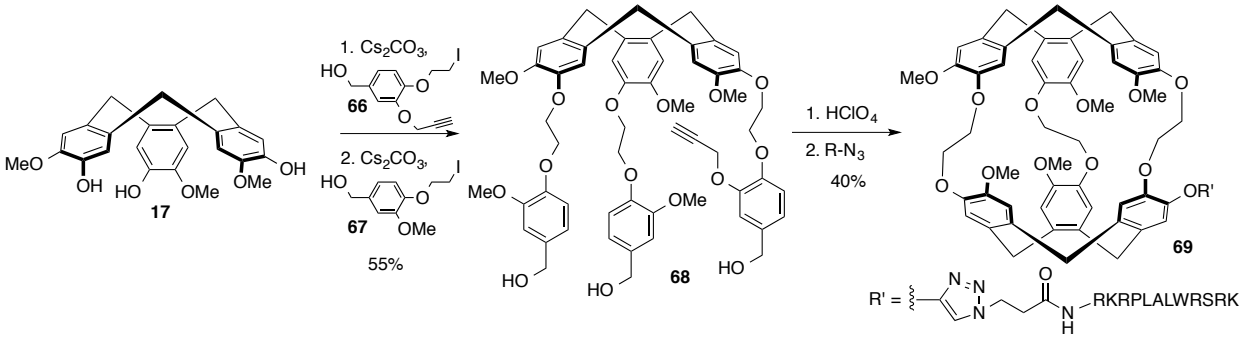


65

developed the first enzymatically sensitive Xe biosensor.[39] The authors developed a cryptophane

with an available linker to append an enzyme substrate as shown in Scheme 12. The known cyclophane (**17**) is first elaborated by etherification with the alkyl halides **66** and **67** to give cryptophane precursor **68**. Cyclization of the three pendant aromatic rings completed the cryptophane core, after which a twelve amino acid peptide chain was attached to give **69**. This peptide serves as a substrate for the MMP-7 enzyme, known to be upregulated in many cancers.

Scheme 12. Synthesis of Peptide-Linked Cryptophane **68**.

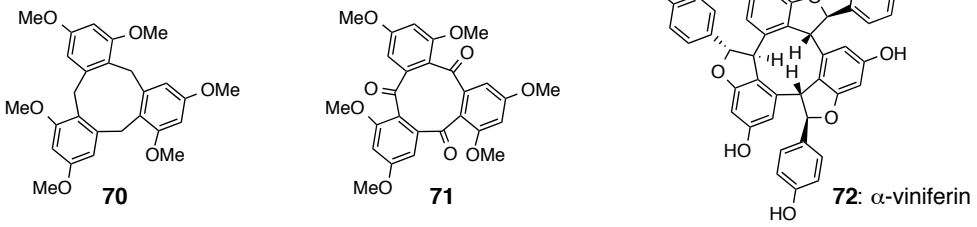


Upon cleavage of that substrate by the MMP-7 enzyme, a noticeable shift was seen in the ^{129}Xe NMR, thus allowing for detection of the presence of that enzyme and potentially early diagnosis of the cancers for which it is indicative. By sensing a catalytic event rather than stoichiometric binding as many sensors do, this method represents a fundamental improvement in biomarker detection. While there are other applications of cryptophanes, the purpose described above represents the most exciting and heavily investigated vein of research. As noted with the other applications of molecules of this type, control and options in their generation is paramount to extracting the maximum utility and potency out of their unique properties. With this in mind, we present our contributions to this exciting field that grew out of work as described in the preceding chapter.

4.5 Synthesis of a New [1.1.1] Orthocyclophane and Achieving the Elusive Triketone

In our efforts toward the synthesis of 9-membered ring containing resveratrol-based natural products, of which α-viniferin (**72**) is a representative example,[40] we sought triketone **71** as a key intermediate shown in Figure 9. We hoped that simultaneous elaboration of all three carbonyl moieties would lead to a rapid construction of the desired natural products. Our first

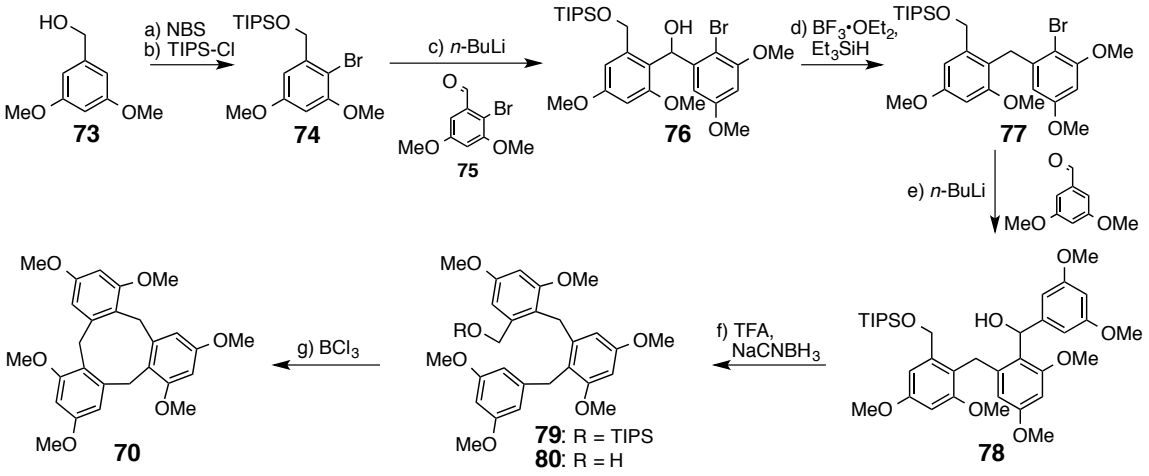
Figure 9. Compounds of Interest En Route to α-Viniferin.



attempted route to the triketone was through cyclotriveratrylene analog **70**, after which benzylic oxidation would be employed for global oxidation of the methylene positions. Although simple trimerization of appropriately substituted benzylic alcohols using an acid catalyst had produced many cyclotriveratrylene analogs (see Section 4.3.1), we unfortunately did not observe the desired product in any detectable quantity upon employing the same, previously published conditions. Common to all of the successful instances of this one step trimerization is the presence of a methoxy substituent *para-* to the benzylic alcohol, a group which assists in cation generation, thus increasing the reaction rate.

As a result we embarked on an alternate, stepwise strategy to achieve the desired intermediate as shown in Scheme 13. Bromination and protection of the benzylic alcohol **73** gave coupling precursor **74**. This compound, upon lithiation, was then added into aldehyde **75** to give bisbenzylic alcohol **76**. Subsequent reductive removal of the hydroxyl group furnished the methylene bridge of **77**. Following this two-step sequence, some of the bromine introduced with aldehyde **75** had been replaced by hydrogen. This outcome likely resulted from lithium transfer

Scheme 13. Synthesis of **70** and Attempted Oxidation.



Reagents and Conditions: a) NBS, CH_2Cl_2, 0 ºC, 12 h, 99%; b) TIPS-Cl, 1-Me-imid., I_2, 25 ºC, 1 h, 95%; c) *n*-BuLi, **75**, -78 ºC, 12 h, 64%; d) BF_3•OEt_2, Et_3SiH, CH_2Cl_2, -78 ºC, 76%; e) *n*-BuLi, Ar-CHO, -78 ºC, 12 h, 69%; f) TFA, $NaCNBH_3$, CH_2Cl_2, 30 min, 57% **79**, 19% **80**; g) BCl_3, CH_2Cl_2, 25 ºC, 60%.

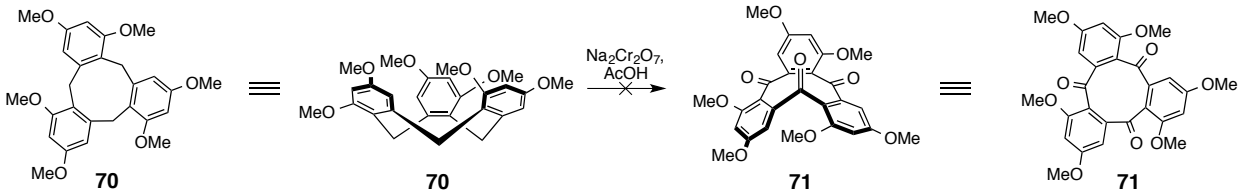
and protonation upon work-up from the coupling step; some reduction in the subsequent step may have also occurred. In any event, the newly obtained bromide was then lithiated and added into 3,5-dimethoxybenzaldehyde with the resulting alcohol **78** reduced to give cyclization precursor **79**/**80**. We found that treatment with BCl_3 accomplished the desired cyclization to **70** in 60% yield, with another 20% of the material recovered as the uncyclized benzylic chloride (structure not shown). Prolonged exposure led to overall higher yields of 9-membered ring products, however, they generally had varying degrees of demethylation; this outcome could be remedied fairly easily with subsequent exposure to MeI.

Overall, this result was highly gratifying as we had not only generated the core, carbon framework of our desired natural product, but we had also synthesized an entirely new cyclotriveratrylene analog. Furthermore, our method for constructing **70** could be adopted as a general approach for the synthesis of any [1.1.1]-orthocyclophane unobtainable by the conventional, one step acid-catalyzed method. Given the addition of each aromatic ring individually, this strategy could also provide a way for preparing analogues with differentially substituted aromatic rings fused to the 9-membered ring core. We are currently developing

substrates as proof of principle for this claim incorporating alternate aromatic moieties into the same 9-membered ring final structures.

Pressing forward, we were now positioned to begin benzylic oxidation attempts as shown in Scheme 14. We first began with chromic acid as described by the examples in Section 4.3.4 but unfortunately we observed minimal oxidation in very low yield. Employment of other conventional benzylic oxidation strategies were likewise met with poor conversion. Much like

Scheme 14. Failed Oxidation of **70** To Triketone **71**.

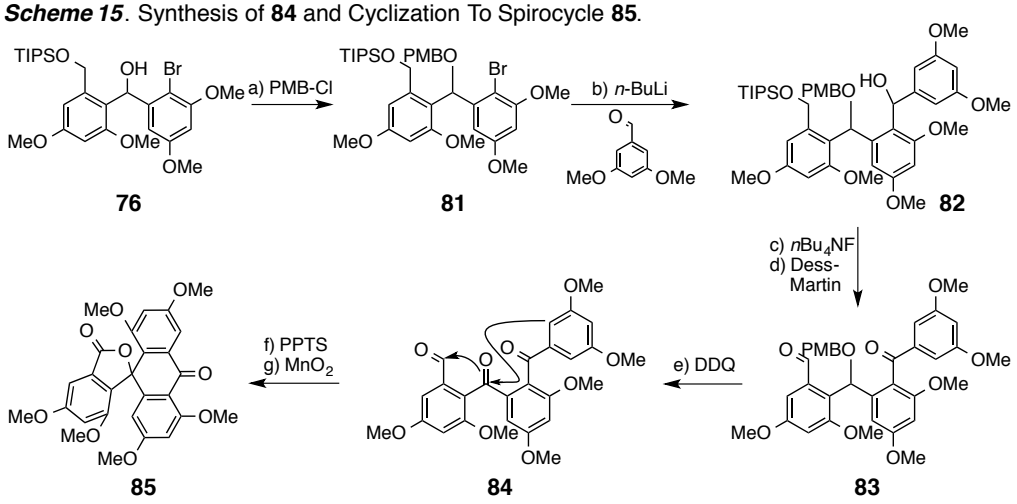


cyclotriveratrylene itself, our substrate **70** inhabits a rigid crown conformation as indicated by the well-resolved methylene protons in its ^{1}H NMR spectrum as well as X-ray crystallographic analysis. This renders the normal orbital alignment associated with a benzylic position, from which the unique reactive properties of that position are derived, as irrelevant since those orbitals are held strictly out of conjugation with the neighboring rings. Oxidation of cyclotriveratrylene, however, is successful so this obstacle is apparently overcome. We are then left to examine the precise differences between these two substrates. Electronically, they are quite similar, but the positioning of a methoxy group *ortho*- to the bridging methylene in **70** invokes a considerable steric component. This function may either serve to block incoming oxidants or increase the energy barrier for conformational inversion due to the steric interactions that it would incur. Since this limited flexibility may make proper orbital alignment for benzylic oxidation fleetingly available in cyclotriveratrylene **3**, a higher energy barrier in the case of **70** would then decrease the frequency of that event, also resulting in slower benzylic oxidation. In any case, we were unsuccessful in our attempts to generate the desired triketone (**71**), or any useful degree of

oxidation, directly from **70** and proceeded instead to an alternate route for its synthesis.

As shown in Scheme 15, we sought to pre-install the desired carbonyls before 9-membered ring formation so as to obviate the need for any subsequent benzylic oxidation. Various protecting group iterations were attempted during the development of this sequence, with the shown approach being the most successful. Thus, from TIPS protected bromide **76**, obtained as described in Scheme 13, the free hydroxyl group is protected as a *p*-methoxybenzyl

Scheme 15. Synthesis of **84** and Cyclization To Spirocycle **85**.



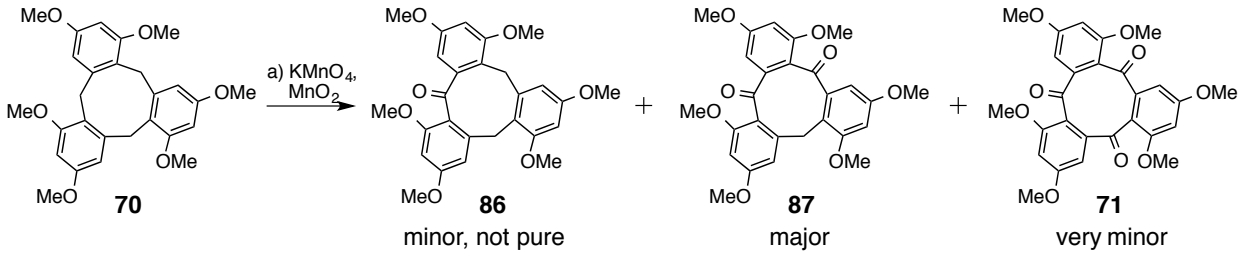
Reagents and Conditions: a) NaH, PMB-Cl, *n*-Bu_4NI, THF, 25 ºC, 12 h, 97%; b) *n*-BuLi, Ar-CHO, THF, -78 ºC, 9 h, 76%; c) *n*-Bu_4NF, THF, 25 ºC, 1 h, 92%; d) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 1 h, 99%; e) DDQ, CH_2Cl_2, 25 ºC, 1.5 h, 99%; f) PPTS, CH_2Cl_2, 25 ºC, 1 h; g) MnO_2, CH_2Cl_2, 25 ºC, 30 min, 52% from **84**.

ether to give **81**. Lithiation and addition of the final aromatic ring proceeded smoothly, furnishing triaryl piece **82** after which the TIPS group was removed and the two free hydroxyl groups oxidized to their corresponding carbonyl groups with Dess-Martin periodinane, giving **83** in 69% overall yield from **81**. Although it would seem more logical to first remove the PMB protecting group and oxidize all three alcohol simultaneously at first glance, it turned out that this deprotection was only effective if the primary alcohol was either protected or already oxidized to an aldehyde. Alternatively, the ketoaldehyde **83** could be treated with DDQ, not only removing the protecting group, but also oxidizing the resultant free alcohol to a ketone, an unexpected, but welcomed overoxidation.

At this point, we first attempted nine membered ring formation by treating diketoaldehyde **84** with various Lewis and Brønsted acids. Unfortunately, all of these attempts gave the same product after subsequent oxidation, namely spirocyclic lactone **85**. We believe this material resulted from the indicated mechanism; it is possible, however, that 9-membered ring formation occurred first and was followed by transannular rearrangement to the spirocyclic structure as detailed in a previous case with cyclotriveratrylene (see Section 4.3.4). Resigned to the unattainability of the desired triketone **71**, we engaged other strategies towards the synthesis of 9-membered ring containing natural products as detailed in Chapter 3.

Quite some time after pursuing the triketone, a publication in 2013 came to our attention showing new conditions for the oxidation of cyclotriveratrylene using a combination of $KMnO_4$ and MnO_2 in refluxing pyridine.[41] The authors report a much higher yield of oxidation to the mono- and di-ketones than any previous methods and, for the sake of completeness, we attempted oxidation of **70** using these same conditions as shown in Scheme 16. Much to our surprise, the TLC of the reaction mixture showed three clean, distinct product spots which, upon isolation, turned out to be the monoketone **86**, diketone **87**, and a third, most polar compound, showing no methylene peaks in its ^1H NMR spectrum. In fact, unlike the mono and diketones, this compound showed symmetry with only two aromatic peaks and two methyl peaks. Seeing

Scheme 16. Successful Oxidation of **70**.

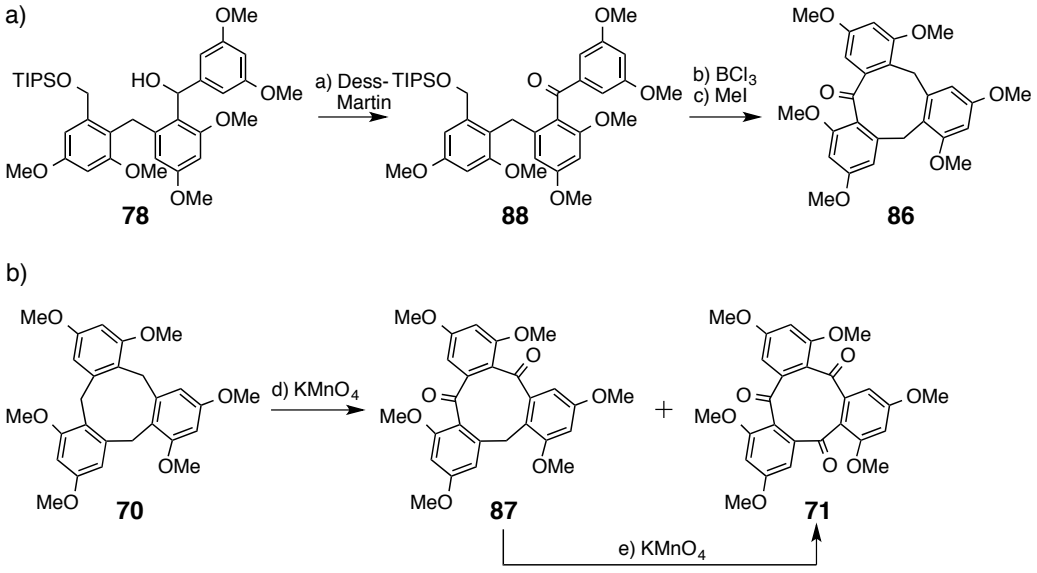


Reagents and Conditions: a) $KMnO_4$, MnO_2, pyr., 100 ºC, 24 h.

as the mass spectral data was consistent with a triketone oxidation state we then concluded that

we had synthesized the long sought and elusive triketone **71**. This conclusion was later supported by X-ray crystallography. The diketone **87** was, by a large margin, the most prominent product of the reaction and the monoketone **86**, despite being a single spot on the TLC, was actually quite impure upon isolation. A pure sample of the monoketone was obtained, albeit in poor yield, from cyclization of compound **88** as shown in Scheme 17a. We later found that by using pure $KMnO_4$, better throughput could be achieved, though still favoring the diketone as outlined in Scheme 17b. Interestingly, in this procedure some starting **70** was recovered, but no trace of the monoketone was observed. Based on these collective experiments

Scheme 17. a) Synthesis of Pure Monoketone; b) Improved Oxidation of **70**.

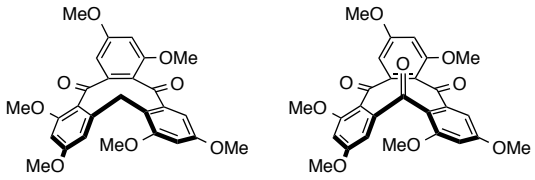


Reagents and Conditions: a) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 25 ºC, 30 min; b) BCl_3, CH_2Cl_2, 25 ºC, 20 h; c) MeI, K_2CO_3, acetone, 56 ºC, 12 h, 23% from **78**; d) $KMnO_4$, pyr., 130 ºC sealed tube, 72 h, 32% **87**, 15% **71**; e) $KMnO_4$, pyr. 130 ºC sealed tube, 72 h, 20% **71**, 30% recovered **87**.

we conclude that the first and third oxidations occur slowly, while the second oxidation is very rapid, thereby accounting for no recovery of the monoketone. Resumbission of the diketone **87** to the reaction conditions gave additional conversion to triketone **71**. For reasons presently unclear, in each $KMnO_4$ oxidation shown in Scheme 17b we could cleanly recover only approximately 50-55% of the material balance, with no other products or decomposition

observed. As observed for all other ketone containing cyclotriveratrylene analogues, X-ray crystallography shows the diketone and triketone to inhabit a saddle conformation as shown in Figure 10. This is likely true for the monoketone as well based on precedent, although an X-ray

Figure 10. Conformation of Diketone **87** and Triketone **71** As Shown by X-Ray Diffraction.

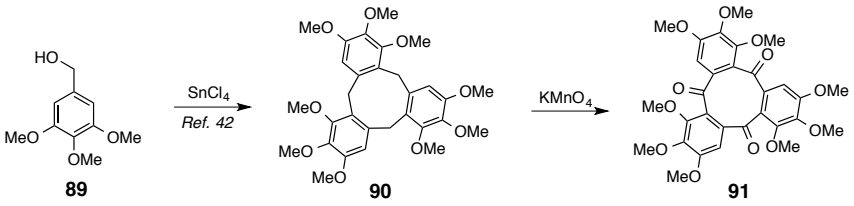


87 **71**

structure was not obtained in that case (Note: Some unresolved disorder in the X-ray crystal structure of **71** was present, however, the data was sufficiently clear for confident structural and conformational assignment in the solid state). It may seem curious that we did not see rearrangement to the spirocyclic lactone **85** (Scheme 15) as observed with very similar substrates; we can confirm that no trace of such a product was obtained, having already synthesized **85** by other means. Perhaps the energy of the intermediates in that rearrangement became prohibitively high with the methoxy groups now *ortho-* to the methylene positions, thus causing a drastic increase in steric interactions versus the previous cases where no such substitution is present. Ironically, it seems that the same aspect of substrate **70** which hindered earlier benzylic oxidation also prevented undesired rearrangement once the oxidation was achieved.

In order to test this hypothesis and also to access a triketone structure more readily, we synthesized cyclotriveratrylene analog **90** as shown below in Scheme 18. The commericially available 3,4,5-trimethoxybenzyl alcohol starting material **89** was cyclized to the corresponding nine membered ring using a published procedure.[42] Subsequent oxidation using identical conditions as before successfully produced the corresponding triketone **91** in a yield of 8% along

Scheme 18. Synthesis of Triketone **91**.



with the diketone in 42% yield (not shown). This result supports our hypothesis that the presence of a methoxy group adjacent to the methylene bridges rearrangement of the triketone product.

4.6 Conclusion

In summary, we have developed a unique approach for cyclotriveratrylene analogues that are ineligible for the traditional one-step synthetic approach. Additionally, we have accomplished the first synthesis, isolation, and characterization of a [1.1.1]-orthocyclophane triketone. Efforts to elaborate this triketone towards our initial goals of natural product synthesis are still underway; however, at present, we believe this work constitutes a significant contribution to the realm of [1.1.1]-orthocyclophane, and more specifically, cyclotriveratrylene chemistry. This result not only conquers a long-standing challenge in this field, it opens up a fundamentally unique mode of elaboration and manipulation to this exciting class of molecules. The need for optimal control over the properties of these cyclotriveratrylene analogues is critical to their effective use in all of the applications surveyed (Section 4.4) and this finding lays the foundation for overcoming a deficiency in current methodology for their preparation. Such a result illuminates the value of natural product total synthesis as it so often uncovers solutions previously hidden for problems outside its main goal. We are excited to see the future of this triketone and its use to [1.1.1] orthocyclophane based applications.

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4.7 References

1. (a) S. Cannizzaro, *Ann. Chem. Pharm.* **1854**, *90*, 252–254; (b) Cannizzaro, S. *Ann. Chem. Pharm.* **1854**, *92*, 113 – 117.

2. P. Sabatier, J.-B. Senderens, *Compt. Rend.* **1900**, *130*, 250 - 252.

3. R. L. Shriner, A. Berger, *J. Org. Chem.* **1941**, *6*, 305 - 318.

4. J. P. Grealis, H. Muller-Bunz, M. Casey, M. J. McGlinchey, *Tetrahedron Lett.* **2008**, *49*, 1527 - 1530.

5. G. M. Robinson, *J. Chem. Soc. Trans.* **1915**, 267 - 276.

6. A. S. Lindsay, *J. Chem. Soc.* **1965**, 1685 - 1692.

7. T. Sato, K. Uno, M. Kainosho, *J. Chem. Soc., Chem. Commun.* **1972**, 579 - 580.

8. C. Schmuck, W. Wienand, *Synthesis* **2002**, *5*, 655 - 663.

9. J. L. Scott, D. R. MacFarlane, C. L. Raston, C. M. Teoh, *Green Chem.* **2000**, *2*, 123 - 126.

10. Y. M. Vargas-Rodriguez, M. Vargas, R. Miranda, B. Francisco, O. Nogues, J. A. Morales-Serna, M. Salmon, *Org. Commun.* **2012**, *5*, 58 - 63.

11. T. Brotin, V. Roy, J.-P. Dutasta, *J. Org. Chem.* **2005**, *70*, 6187 - 6195.

12. V. Percec, M. R. Imam, M. Peterca, D. A. Wilson, P. A. Heiney, *J. Am. Chem. Soc.* **2009**, *131*, 1294 - 1304.

13. R. M. Thomas, G. H. Mohan, D. S. Iyengar, *Tet. Lett.* **1997**, *38*, 4721 - 4724

14. X.-N. Han, J.-M. Chen, Z.-T. Huang, Q.-Y. Zheng, *Eur. J. Org. Chem.* **2012**, 6895 - 6903.

15. (a) A. Chakrabarti, H. M. Chawla, G. Hundal, N. Pant, *Tetrahedron* **2005**, *61*, 12323 - 12329; (b) J.-R. Song, Z.-T. Huang, Q.-Y. Zheng, *Tetrahedron* **2013**, *69*, 7308 - 7313.

16. T. Yamato, N. Sakaue, *J. Chem. Research* **1997**, *S*, 440 - 441.

17. J. Canceill, A. Collet, *J. Chem. Soc. Chem. Commun.* **1983**, 1145 - 1147

18. R. C. Cookson, B. Halton, I. D. R. Stevens, *J. Chem. Soc. (B)* **1968**, 767.

19. A. Collet, J. Gabard, *J. Org. Chem.* **1980**, *45*, 5400 - 5401.

20. J. E. Baldwin, D. P. Kelly, *Chem. Commun.* **1968**, 1664 - 1665.

21. J. Bergman, S. Hogberg, J.-O. Lindstrom, *Tetrahedron* **1970**, *26*, 3347 - 3352.

22. M. Santoso, K. Somphol, N. Kumar, D. StC. Black, *Tetrahedron* **2009**, *65*, 5977 - 5983.

23. J. E. Riby, C. Feng, Y.-C. Chang, C. M. Schaldach, G. L. Firestone, L. F. Bjeldanes, *Biochemistry*, **2000**, *39*, 910 - 918.

24. A. Treibs, F.-H. Kreuser, N. Haberle, *Liebigs Ann. Chem.* **1970**, *733*, 37 - 43.

25. Y. Fumoto, H. Uno, S. Ito, Y. Tsugumi, M. Sasaki, Y. Kitawaki, N. Ono, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2977 - 2981.

26. K. G. Untch, *J. Am. Chem. Soc.* **1963**, *85*, 345 - 346.

27. A. Pleschke, J. Geier, M. Keller, J. Worth, L. Knothe, H. Prinzbach, *Eur. J. Org. Chem.* **2007**, 4867 - 4880.

28. M. J. Hardie, *Chem. Soc. Rev.* **2010**, *39*, 516 - 527.

29. J. W. Steed, P. C. Junk, J. L. Atwood, M. J. Barnes, C. L. Raston, R. S. Burkhalter, *J. Am. Chem. Soc.* **1994**, *116*, 10346 - 10347.

30. E. Huerta, G. A. Metselaar, A. Fragoso, E. Santos, C. Bo and J. de Mendoza, *Angew. Chem. Int. Ed.*, **2007**, *46*, 202.

31. (a) K. T. Holman, M. M. Halihan, S. S. Jurisson, J. L. Atwood, R. S. Burkhalter, A. R. Mitchell and J. W. Steed, *J. Am. Chem. Soc.* **1996**, *118*, 9567; (b) J. A. Gawenis, K. T. Holman, J. L. Atwood and S. S. Jurisson, *Inorg. Chem. 2002*, *41*, 6028.

32. M. Garcia-Leon, *J. Nuc. Radiochem. Sci.* **2005**, *6*, 253 - 259.

33. O. Reynes, F. Maillard, J.-C. Moutet, G. Royal, E. Saint-Aman, G. Stanciu, J.-P. Dutasta, I. Gosse and J.-C. Mulatier, *J. Organomet. Chem.* **2001**, *356*, 637 – 639.

34. B. F. Abrahams, N. J. FitzGerald, T. A. Hudson, R. Robson and T. Waters, *Angew. Chem. Int. Ed.* **2009**, *48*, 3129.

35. D. Xu, R. Warmuth, *J. Am. Chem. Soc.* **2008**, *130*, 7520 - 7521.

36. T. Brotin, J.-P. Dutasta, *Chem. Rev.* **2009**, *109*, 88 - 130.

37. J. Wolber, I. J. Rowland, M. O. Leach, A. Bifone, *Appl. Magn. Reson.* **1998**, *15*, 343 - 352.

38. K. Bartik, M. Luhmer, J.-P. Dutasta, A. Collet, J. Reisse, *J. Am. Chem. Soc.* **1998**, *120*, 784.

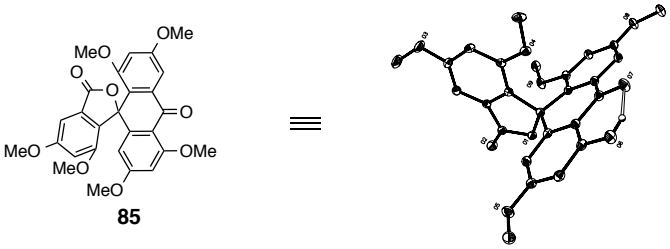
39. Q. Wei, G. K. Seward, P. A. Hill, B. Patton, I. E. Dimitrov, N. N. Kuzma, A. J. Dmochowski, *J. Am. Chem. Soc.* **2006**, *128*, 13274 - 13283.

40. R. J. Pryce, P. Langcake, *Phytochemistry* **1977**, *16*, 1452 - 1454.

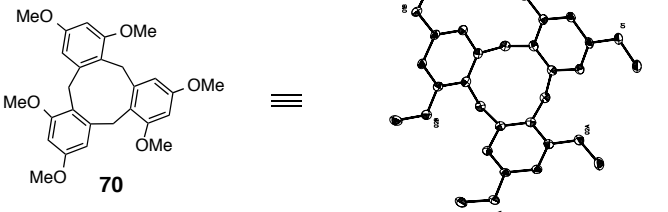
41. S. R. S. Sarsah, M. R. Lutz Jr., M. Zeller, D. S. Crumrine, D. P. Becker, *J. Org. Chem* **2013**, *78*, 2051 - 2058.

42. Y. Ding, B. Li, G. Zhang, *ARKIVOC* **2007**, *14*, 322-326.

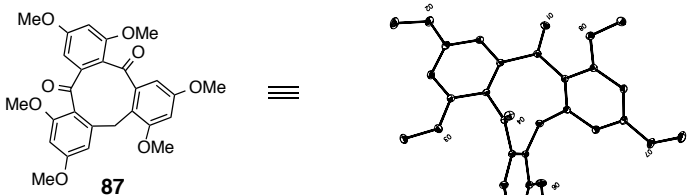
Relevant X-Ray Crystal Structures:



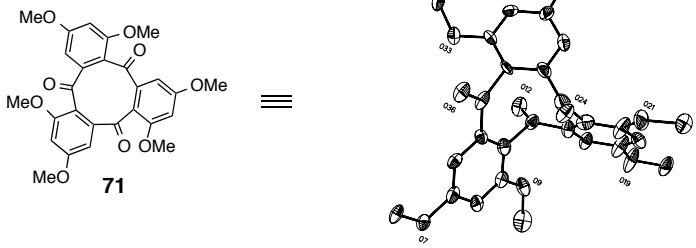
85



70



87



71

4.8 Experimental Procedures

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), acetonitrile (MeCN), toluene, benzene, diethyl ether (Et_2O) and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and either an aqueous solution of ceric ammonium sulfate and ammonium molybdate and heat or an aqueous solution of potassium permanganate and sodium bicarbonate and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-300, DRX-400, DMX-500 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, br = broad, AB = AB quartet, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using the MALDI (matrix-assisted laser-desorption ionization) technique.

Alcohol 76. n-BuLi (43.9 mL, 1.6 M in THF, 70.3 mmol, 1.3 equiv) was added slowly

over the course of 5 min to a solution of bromide **74** (21.8 g, 54.0 mmol, 1.0 equiv) in THF (300 mL) at –78 °C. After 20 min of stirring at –78 °C, a solution aldehyde **75** (17.2 g, 70.3 mmol, 1.3 equiv) in THF (100 mL) was added slowly at –78 °C, and the resultant mixture was stirred for 1 h at –78 °C, warmed slowly to 25 °C, and stirred for an additional 8 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous NH_4Cl (250 mL), poured into water (100 mL), and extracted with EtOAc (3 x 300 mL). The combined organic layers were then washed with brine (200 mL), dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc 9:1) to give alcohol **76** (19.7 g, 64% yield) as a yellow oil.

Bromide 77. BF_3•OEt_2 (12.4 mL, 97.8 mmol, 3.0 equiv) was added slowly over the course of 10 min to a solution of alcohol **76** (18.6 g, 32.6 mmol, 1.0 equiv) and triethylsilane (18.9 g, 163.0 mmol, 5.0 equiv) in CH_2Cl_2 (300 mL) at -78 °C. The resultant solution was allowed to warm slowly to 25 °C over the course of 1 hour and upon completion the reaction contents were quenched by the addition of water (100 mL), extracted with CH_2Cl_2 (2 x 200 mL). The combined organic layers were then dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc 19:1) to give **77** (11.8 g, 65% yield) as well as an additional portion of desilylated **77** which, upon silylation, gave additional **77** (2.1 g, 11% yield) as a pale yellow oil. **77**: R_f = 0.59 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 2941, 2864, 1603, 1587, 1488, 1452, 1428, 1415, 1323, 1298, 1224, 1198, 1159, 1145, 1123, 1061, 1022, 996, 947, 928, 882, 839, 828, 794, 736, 682, 658, 647, 631, 502; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (d, J = 2.3 Hz, 1 H), 6.44 (d, J = 2.4 Hz, 1 H), 6.32 (d, J = 2.7 Hz, 1 H), 5.90 (d, J = 2.7 Hz, 1 H), 4.61 (s, 2 H), 3.97 (s, 2 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.76 (s, 3 H), 3.58 (s, 3 H), 1.09-1.03 (m, 3 H), 1.02 (s, 12 H), 1.00 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7,

159.6, 158.6, 156.6, 142.8, 142.2, 116.2, 105.9, 105.2, 102.6, 97.2 (2C), 62.8, 56.5, 55.9, 55.3, 55.3, 30.8, 18.1, 12.1; HRMS (FAB+) calcd for $C_{27}H_{41}O_5BrSi^+$ [M^+] 552.1907, found 552.1906.

Tri-aryl Piece 79. *n*-BuLi (1.2 mL, 1.6 M in THF, 1.85 mmol, 1.3 equiv) was added slowly over the course of 5 min to a solution of diaryl bromide **77** (0.788 g, 1.42 mmol, 1.0 equiv) in THF (20 mL) at –78 °C. After 20 min of stirring at –78 °C, a solution of 3,5 dimethoxybenzaldehyde (0.473 g, 70.3 mmol, 1.3 equiv) in THF (8 mL) was added slowly at –78 °C, and the resultant mixture was stirred for 1 h at –78 °C, warmed slowly to 25 °C, and stirred for an additional 8 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous NH4Cl (10 mL), poured into water (10 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layers were then washed with brine (20 mL), dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc 3:1) to give alcohol **78** (0.629 g, 69% yield) as a pale yellow oil. Pressing forward, trifluoroacetic acid (0.17 mL, 2.23 mmol, 3.0 equiv) was added slowly to a solution of alcohol **78** (0.477 g, 0.74 mmol, 1.0 equiv) and $NaCNBH_3$ (1.40 g, 22.3 mmol, 30 equiv) in CH_2Cl_2 (20 mL) at 25 °C and the resulting solution allowed to stir for 30 min. Upon completion, the reaction contents were quenched by the addition of water (10 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were then dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc 19:1→4:1) to give **79** (0.264 g, 57% yield) in addition to desilylated **80** (66.0 mg, 19% yield) both as pale yellow oils. **79**: R_f = 0.63 (silica gel, hexanes/EtOAc, 4:1); IR (film) νmax 2996, 2938, 2863, 2835, 1593, 1459, 1426, 1374, 1314, 1200, 1144, 1058, 1012, 995, 947, 911, 882, 827, 734, 685, 660, 494, 458 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 6.88 (d, J = 2.4 Hz, 1 H), 6.39 (d, J = 2.4 Hz, 1 H), 6.36 (d, J = 2.0 Hz, 2 H), 6.34 (d, J = 2.4 Hz, 1 H), 6.27 (t, J = 2.0 Hz, 1 H), 5.83 (d, J = 2.4 Hz, 1 H), 4.49 (s, 2 H), 4.07

(s, 2 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 2 H), 3.74 (s, 6 H), 3.69 (s, 3 H), 3.59 (s, 3 H), 0.99 (m, 21 H); ^{13}C NMR (100 MHz, CDCl3) δ 160.7, 159.4, 159.1, 158.6, 158.6, 144.0, 142.7, 141.6, 119.4, 116.3, 106.6, 104.4, 102.2, 97.4, 97.1, 95.8, 62.5, 55.8, 55.7, 55.3, 55.2, 55.1, 31.2, 27.5, 18.1, 12.1; HRMS (FAB+) calcd for $C_{36}H_{52}O_7Si^+$ [M^+] 624.3482, found 624.3840.

9-Membered Ring 70. BCl_3 (0.30 mL, 1.0 M in CH_2Cl_2, 0.30 mmol, 2.5 equiv) was added to a solution of **79** (72 mg, 0.12 mmol, 1.0 equiv) in CH_2Cl_2 (7 mL) at 25 °C and stirred for 5 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (2 mL), poured into water (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) to give 70 (31 mg, 60% yield) as an off-white solid. **70**: R_f = 0.55 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2989, 2934, 2830, 1601, 1461, 1417, 1341, 1306, 1281, 1237, 1203, 1163, 1139, 1081, 949, 888, 849, 818, 770, 727, 662, 644, 568, 547, 528, 508, 491, 467 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (s, 3 H), 6.30 (s, 3 H), 4.50 (d, J = 10.8 Hz, 3 H), 4.16 (d, J = 10.8 Hz, 3 H), 3.88 (s, 9 H), 3.77 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 158.3, 142.7, 120.8, 107.3, 97.0, 55.3, 55.2, 29.2; HRMS (FAB+) calcd for $C_{27}H_{30}O_6^+$ [M^+] 450.2042, found 450.2046.

Bromide 81. Sodium hydride (0.450 g, 60% dispersion in mineral oil, 6.60 mmol, 2.5 equiv) was added portionwise to a solution of alcohol **76** (1.50 g, 2.64 mmol, 1.0 equiv) in THF (20 mL) and DMF (2 mL) at 0 °C. After 10 min of stirring, 4-methoxybenzyl chloride (0.40 mL, 2.90 mmol, 1.1 equiv) was added followed by *n*-Bu_4NI (98.0 mg, 0.264 mmol, 0.1 equiv) as a single portion and the reaction mixture allowed to warm slowly to 25 °C and stir for an additional 12 h. Upon completion, the reaction mixture was quenched carefully with water (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were then wash with

brine (20 mL), dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 19:1→9:1) to give **81** (1.76 g, 97% yield) as a colorless oil. **81**: R_f = 0.53 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 2940, 2864, 1603, 1586, 1513, 1453, 1424, 1388, 1317, 1302, 1247, 1222, 1199, 1172, 1159, 1142, 1111, 1059, 1037, 1025, 1012, 997, 962, 882, 858, 823, 732, 683, 659, 651; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2 H), 7.08 (d, J = 2.5 Hz, 1 H), 6.82 (d, J = 8.7 Hz, 2 H), 6.73 (d, J = 2.7 Hz, 1 H), 6.41 (d, J = 2.8 Hz, 1 H), 6.39 (d, J = 2.6 Hz, 1 H), 6.18 (s, 1 H), 4.88 (d, J = 15.2 Hz, 1 H), 4.59 (d, J = 10.6 Hz, 1 H), 4.53 (d, J = 15.2 Hz, 1 H), 4.39 (d, J = 11.0 Hz, 1 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 3.72 (s, 3 H), 1.00-0.97 (m, 21 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 159.3, 159.3, 159.2, 156.8, 144.2, 143.0, 131.0, 129.5, 115.8, 113.7, 106.6, 104.6, 102.3, 98.5, 97.0, 75.6, 70.9, 62.9, 56.5, 55.9, 55.4, 55.4, 55.2, 18.2, 18.2, 12.1; HRMS (FAB+) calcd for $C_{35}H_{49}O_7BrSi^+$ [M^+] 688.2382, found 688.2414.

Ketoaldehyde 83. *n*-BuLi (1.8 mL, 1.6 M in hexanes, 2.88 mmol, 1.1 equiv) was added slowly over the course of 5 min to a solution of **81** (1.76 g, 2.54 mmol, 1.0 equiv) in THF (20 mL) at –78 °C. After 20 min of stirring at –78 °C, a solution of 3,5-dimethoxybenzaldehyde (0.761 g, 4.58 mmol, 1.8 equiv) in THF (10 mL) was added slowly at –78 °C, and the resultant mixture was stirred for 1 h at –78 °C, warmed slowly to 25 °C, and stirred for an additional 8 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous NH_4Cl (10 mL), poured into water (10 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc 4:1) to give alcohol **82** (1.51 g, 76% yield) as a pale yellow oil. Pressing forward, *n*-Bu_4NF (1.40 mL, 1.0 M in THF, 1.40 mmol, 1.2 equiv) was added to a solution of alcohol **82** (0.898 g, 1.16 mmol, 1.0 equiv) in THF (15 mL) at 25 °C

and stirred for 1 h. Upon completion the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (5 mL), poured into water (5 mL), and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:2) to give the resultant diol (0.659 g, 92% yield) as a pale yellow oil. Pressing forward, $NaHCO_3$ (1.03 g, 12.3 mmol, 10 equiv) followed by Dess-Martin periodinane (1.30 g, 3.07 mmol, 2.5 equiv) were added as a single portions to a solution of the diol (0.763 g, 1.23 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 25 °C and stirred for 1 h. Upon completion the reaction contents were quenched by the addition of saturated aqueous Na_2SO_3 (5 mL) and stirred vigorously for 5 min then poured into water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated to give keto-aldehyde **83** (0.751 g, 99% yield) as a yellow/orange viscous oil. **83**: R_f = 0.16 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 2940, 2866, 1687, 1667, 1599, 1583, 1514, 1457, 1425, 1391, 1369, 1315, 1299, 1267, 1248, 1224, 1200, 1175, 1153, 1060, 1049, 1033, 1009, 990, 957, 935, 883, 844, 831, 821, 770, 759, 742, 677, 648, 605, 587, 569, 516, 497; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1 H), 6.98 (br s, 1 H), 6.77 (br s, 2 H), 6.77-6.72 (m, 2 H), 6.59 (S, 1 H), 6.56 (d, J = 9.0 Hz, 2 H), 6.48 (t, J = 2.2 Hz, 1 H), 6.39 (d, J = 1.9 Hz, 1 H), 6.34 (s, 1 H), 6.24 (br s, 1 H), 4.16 (d, J = 10.6 Hz, 1 H), 4.10 (d, J = 10.7 Hz, 1 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.70 (s, 3 H), 3.70 (s, 6 H), 3.63 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 192.6, 161.1, 160.7, 160.4, 159.4, 158.8, 158.6, 143.7, 140.5, 137.8, 129.6, 129.1, 123.7, 113.3, 113.1, 106.9, 105.3, 105.1, 103.4, 103.0, 97.0, 72.5, 71.2, 56.1, 56.0, 55.6, 55.5, 55.4, 55.3; HRMS (FAB+) calcd for $C_{35}H_{37}O_{10}^+$ [M^+] 617.2387, found 617.2404.

Diketoaldehyde 84. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.691 g, 3.04 mmol,

2.5 equiv) was added to a solution of **83** (0.751 g, 1.22 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) at 25 °C and stirred for 1.5 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and stirred vigorously for 15 min the poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:2) to give diketoaldehyde **84** (0.595 g, 99% yield) as a white foam. **84**: R_f = 0.21 (silica gel, hexanes/EtOAc, 1:1); IR (film) ν_{max} 3007, 2964, 2941, 2841, 1698, 1671, 1595, 1456, 1425, 1319, 1295, 1203, 1152, 1063, 1046, 979, 925, 909, 845, 728, 702, 646, 600; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1 H), 6.90 (d, J = 2.2 Hz, 1 H), 6.86 (d, J = 2.3 Hz, 2 H), 6.78 (d, J = 2.2 Hz, 1 H), 6.71 (d, J = 2.2 Hz, 1 H), 6.58 (t, J = 2.3 Hz, 1 H), 6.48 (d, J = 2.2 Hz, 1 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.77 (s, 6 H), 3.73 (s, 3 H), 3.65 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 194.2, 190.1, 162.4, 161.3, 161.2, 160.7, 159.2, 158.4, 139.8, 139.5, 137.4, 124.0, 122.9, 107.3, 106.9, 105.3, 104.0, 103.8, 102.9, 56.4, 56.1, 55.8 (2C), 55.6 (2C); HRMS (FAB+) calcd for $C_{27}H_{27}O_9^+$ [M^+] 495.1655, found 495.1660.

Spirocycle 85. Pyridinium p-toluene sulfonate (10.0 mg, 0.040 mmol, 2.0 equiv) was added to a solution of **84** (10 mg, 0.020 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at 25 °C and stirred for 1 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL), poured into water (1 mL) and extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and carried on directly without further purification. Pressing forward, MnO_2 (100 mg) was added to a solution of the newly obtained material in CH_2Cl_2 (1 mL) at 25 °C and stirred for 30 min. Upon completion the reaction contents were filtered through a pad of celite, concentrated, and purified by preparative TLC (EtOAc/hexanes, 4:1) to give spirolactone **85** (5.2 mg, 52% yield from **84**) as a white solid.

85: R_f = 0.09 (silica gel, hexanes/EtOAc, 1:1); IR (film) ν_{max} 2939, 2841, 1768, 1663, 1623, 1598, 1575, 1500, 1456, 1436, 1428, 1352, 1319, 1299, 1257, 1233, 1214, 1196, 1148, 1109, 1058, 1040, 1001, 988, 974, 948, 914, 841, 820, 807, 766, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 2.5 Hz, 1 H), 6.98 (d, J = 1.9 Hz, 1 H), 6.54 (d, J = 2.5 Hz, 1 H), 6.49 (d, J = 2.2 Hz, 1 H), 6.44 (d, J = 1.9 Hz, 1 H), 6.23 (d, J = 2.2 Hz, 1 H), 3.98 (s, 3 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.75 (s, 3 H), 3.59 (s, 3 H), 3.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.9, 171.8, 164.1, 162.8, 162.2, 161.1, 158.3, 154.2, 145.0, 136.1, 133.2, 128.9, 117.0, 114.6, 105.3, 104.5, 102.6, 101.8, 99.1, 98.3, 81.4, 56.5, 56.4, 56.0, 55.8, 55.7, 55.6; HRMS (FAB+) calcd for $C_{27}H_{25}O_9^+$ [M^+] 493.1499, found 493.1486.

Ketone 88. Dess-Martin periodinane (90.0 g, 0.212 mmol, 1.2 equiv) was added as a single portion to a solution of alcohol **78** (0.113 g, 0.176 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) at 25 °C and stirred for 1 h. Upon completion the reaction contents were quenched by the addition of saturated aqueous Na_2SO_3 (3 mL) and stirred vigorously for 5 min then poured into water (3 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated to give ketone **88** (0.112 g, 99% yield) as a yellow viscous oil. **88**: R_f = 0.41 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 2940, 2864, 2839, 1669, 1592, 1456, 1425, 1316, 1297, 1200, 1148, 1120, 1060, 989, 947, 927, 882, 837, 810, 770, 737, 681, 653, 501, 462; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, J = 2.2 Hz, 2 H), 6.86 (d, J = 2.3 Hz, 1 H), 6.65 (t, J = 2.2 Hz, 1 H), 6.32 (d, J = 2.4 Hz, 1 H), 6.31 (d, J = 3.4 Hz, 1 H), 5.96 (d, J = 1.7 Hz, 1 H), 4.66 (s, 2 H), 3.81 (s, 6 H), 3.80 (s, 3 H), 3.67 (s, 2 H), 3.66 (s, 3 H), 3.65 (s, 3 H), 3.63 (s, 3 H), 1.11-1.07 (m, 3 H), 1.04 (s, 12 H), 1.02 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 161.4, 160.8, 159.5, 158.6, 158.1, 142.7, 141.3, 140.3, 121.6, 115.6, 107.4, 105.3, 104.9, 102.1, 97.0, 95.8, 62.7, 55.9, 55.6, 55.5, 55.2, 55.2, 27.6, 18.2, 12.1; HRMS

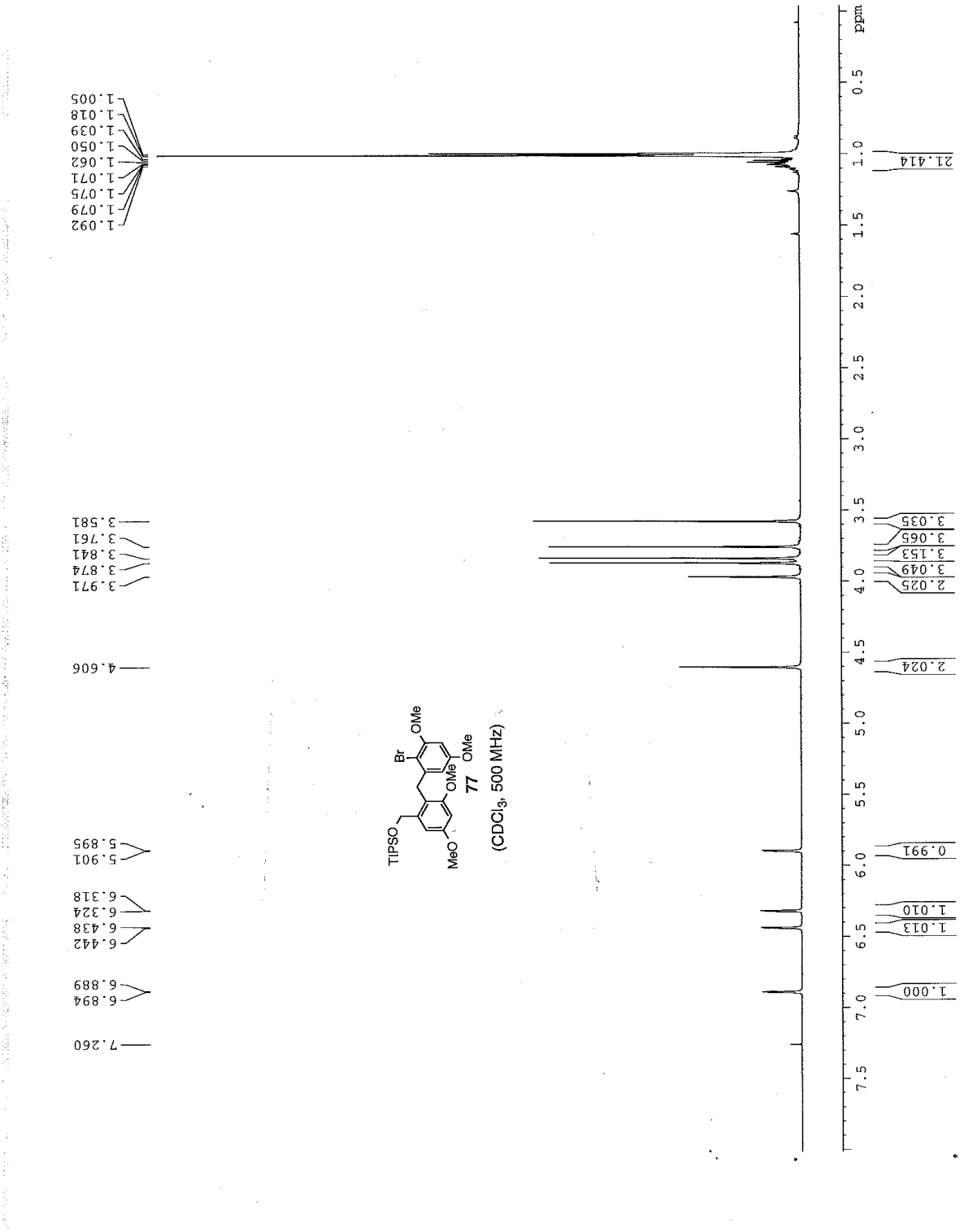
(FAB+) calcd for $C_{36}H_{50}O_8Si^+$ [M^+] 638.3275, found 638.3299.

Mono-ketone 86. BCl_3 (1.76 mL, 1.0 M in CH_2Cl_2, 1.76 mmol, 10 equiv) was added to a solution of ketone **88** (0.112 g, 0.176 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at 25 °C and stirred for 12 h. Upon completion the reaction contents were quenched by the careful addition of saturated aqueous $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and carried on directly without further purification. To a solution of this newly obtained material in acetone (3 mL) was added MeI (0.11 mL, 1.76 mmol, 10 equiv) and powdered K_2CO_3 (0.243 g, 1.76 mmol, 10 equiv) at 25 °C. The reaction mixture was then heated at 56 °C for 6 h. Upon completion, the reaction contents were quenched by the addition of water (3 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), concentrated and purified first by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) followed by preparative TLC ($CHCl_3$/Et_2O, 9:1) to give pure ketone **86** (19 mg, 23% yield) as a colorless foam. **86**: R_f = 0.55 (silica gel, hexanes/EtOAc, 1:1); IR (film) ν_{max} 2999, 2939, 2837, 1643, 1598, 1457, 1418, 1342, 1319, 1304, 1284, 1247, 1198, 1154, 1138, 1082, 1059, 985, 950, 908, 840, 772, 734, 702, 668, 601, 514; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 2.1 Hz, 1 H), 6.59 (d, J = 2.0 Hz, 1 H), 6.50 (d, J = 1.9 Hz, 1 H), 6.38 (d, J =1.7 Hz, 1 H), 6.36 (d, J = 1.9 Hz, 1 H), 6.14 (d, J = 1.8 Hz, 1 H), 3.92 (s, 2 H), 3.90 (s, 2 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.73 (s, 3 H), 3.72 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.3, 162.1, 159.6, 158.7, 158.4, 158.3, 157.3, 141.5, 141.2, 139.7, 125.4, 122.0, 121.6, 109.6, 106.2, 104.2, 103.8, 97.5, 96.8, 56.2, 55.9, 55.9, 55.6, 55.4 (2 C), 30.9, 26.8; HRMS (FAB+) calcd for $C_{27}H_{29}O_7^+$ [M^+] 465.1913, found 465.1902.

Di-ketone 87 and **Tri-ketone 71.** $KMnO_4$ (1.00 g, 6.33 mmol, 140 equiv) was added to a solution of **70** (20.0 mg, 0.044 mmol, 1 equiv) in pyridine (1 mL) at 25 °C. The reaction flask was sealed, placed in a 130 °C oil bath and stirred vigorously for 72 h. Upon completion, the reaction contents were filtered directly through a pad of celite and washed with EtOAc (5 x 10 mL) and CH_2Cl_2 (5 x 10 mL) after which the filtrate was concentrated and purified by preparative TLC (EtOAc/hexanes, 3:2) to give diketone **87** (6.8 mg, 32% yield) and triketone **71** (3.2 mg, 15% yield) each as colorless foams. **87**: R_f = 0.42 (silica gel, hexanes/EtOAc, 1:1); IR (film) ν_{max} 3003, 2939, 2840, 1684, 1660, 1594, 1456, 1419, 1317, 1285, 1206, 1149, 1134, 1080, 1054, 978, 836, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 2.3 Hz, 1 H), 6.63 (d, J = 2.5 Hz, 1 H), 6.59 (d, J = 2.4 Hz, 1 H), 6.50 (d, J = 2.5 Hz, 1 H), 6.30 (d, J = 2.2 Hz, 1 H), 5.92 (d, J = 2.2 Hz, 1 H), 3.90 (s, 2 H), 3.89 (s, 3 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 3.67 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 193.2, 162.5, 161.1, 158.9, 158.7, 156.5, 144.3, 142.5, 138.4, 126.0, 123.0, 121.7, 105.8, 105.0, 104.2, 103.1, 100.9, 97.7, 60.5, 56.2, 56.2, 56.0, 55.8, 55.6, 55.3, 27.8; HRMS (FAB+) calcd for $C_{27}H_{27}O_8^+$ [M^+] 479.1706, found 479.1721. **71**: Rf = 0.19 (silica gel, hexanes/EtOAc, 1:1); IR (film) ν_{max} 2927, 2849, 1689, 1594, 1572, 1459, 1436, 1325, 1252, 1209, 1149, 1081, 1050, 983; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (d, J = 2.3 Hz, 3 H), 6.51 (d, J = 2.3 Hz, 3 H), 3.82 (s, 9 H), 3.75 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 162.2, 157.8, 122.1, 104.2, 101.9, 56.3, 55.8; HRMS (FAB+) calcd for $C_{27}H_{25}O_9^+$ [M^+] 493.1499, found 493.1488.

Triketone 91. $KMnO_4$ (1.00 g, 6.33 mmol, 140 equiv) was added to a solution of **90** (25.0 mg, 0.046 mmol, 1 equiv) in pyridine (1 mL) at 25 °C. The reaction flask was sealed, placed in a 130 °C oil bath and stirred vigorously for 72 h. Upon completion, the reaction contents were filtered directly through a pad of celite and washed with EtOAc (5 x 10 mL) and

CH_2Cl_2 (5 x 10 mL) after which the filtrate was concentrated and purified by preparative TLC (EtOAc/hexanes, 3:2) to give the diketone (11.0 mg, 42% yield) and triketone **91** (2.2 mg, 8% yield) each as colorless foams. Diketone: Rf = 0.28 (silica gel, hexanes/EtOAc, 2:3); IR (film) ν_{max} 2937, 1683, 1652, 1581, 1487, 1452, 1432, 1402, 1388, 1329, 1292, 1254, 1242, 1195, 1146, 1122, 1110, 1086, 1058, 1032, 993, 954, 940, 919, 834, 754, 734, 704, 590; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1 H), 6.82 (s, 1 H), 6.01 (s, 3 H), 3.99 (s, 3 H), 3.91 (s, 3 H), 3.91 (s, 2 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.85 (s, 3 H), 3.67 (s, 3 H), 3.54 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 191.1, 155.8, 153.9, 151.7, 149.9, 149.4, 146.8, 144.0, 141.7, 138.4, 135.6, 131.9, 130.6, 127.5, 127.3, 108.5, 107.7, 107.6, 61.8, 61.8, 61.3, 61.2, 61.1, 61.1, 56.3, 56.1, 55.9, 28.1; HRMS (FAB+) calcd for $C_{30}H_{33}O_{11}^+$ [M^+] 569.2023, found 569.2043. **91**: Rf = 0.16 (silica gel, hexanes/EtOAc, 2:3); IR (film) ν_{max} 2939, 2852, 1692, 1662, 1580, 1486, 1455, 1399, 1323, 1291, 1254, 1195, 1119, 1092, 1030, 989, 938, 810, 733, 613, 572; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 3 H), 3.91 (s, 9 H), 3.87 (s, 9 H), 3.79 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 155.1, 150.4, 145.1, 136.0, 127.7, 106.9, 62.3, 61.3, 56.3; HRMS (FAB+) calcd for $C_{30}H_{31}O_{12}^+$ [M^+] 583.1819, found 583.1816.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3.971
4.606
5.895
5.901
6.318
6.324
6.438
6.442
6.889
6.894
7.260
TIPSO
MeO
OMe
OMe
Br
OMe
77
(CDCl3, 500 MHz)
ppm
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1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
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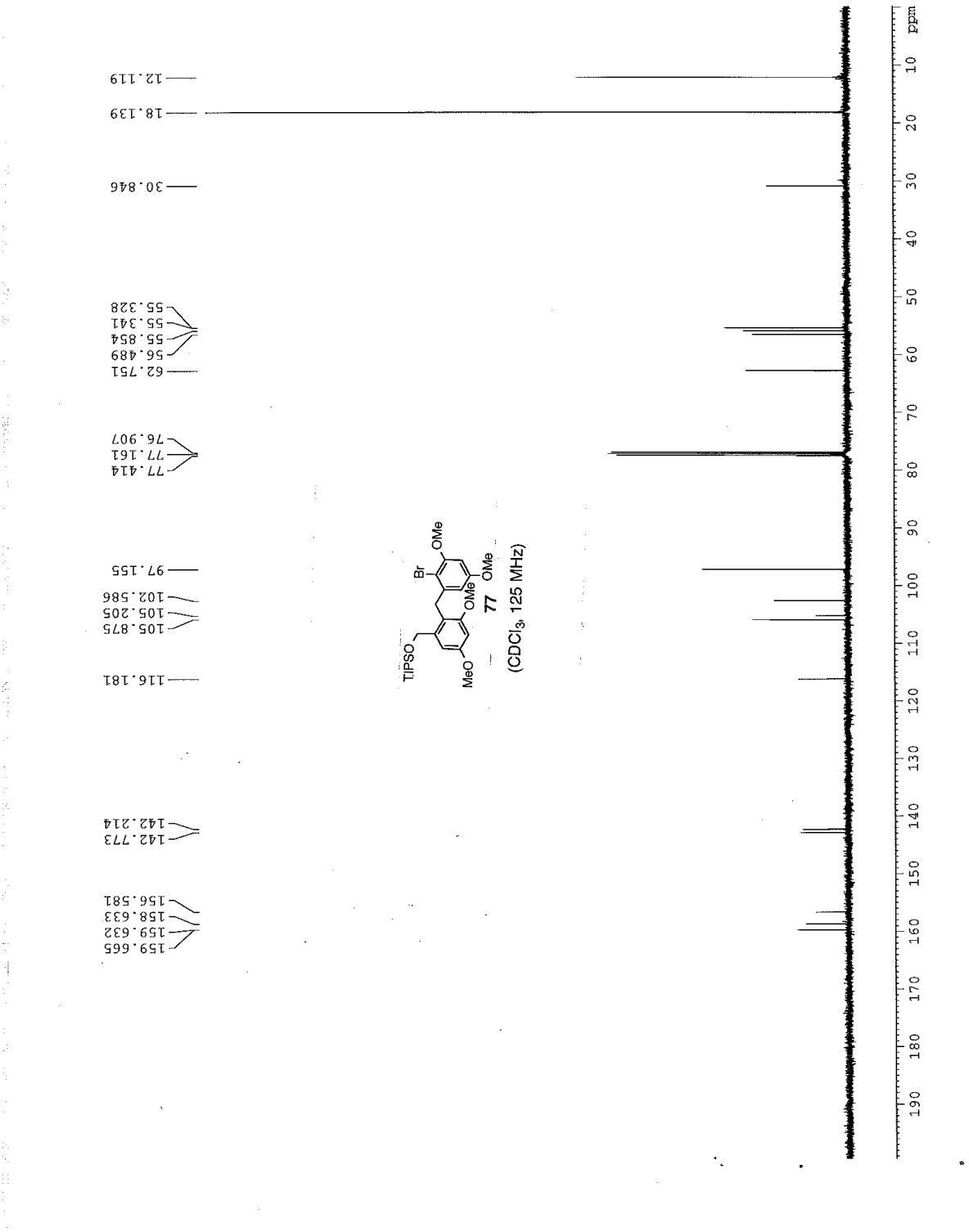
2.024
0.991
1.010
1.013
1.000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105.875
116.181
142.214
142.773
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Br
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OMe
OMe
MeO
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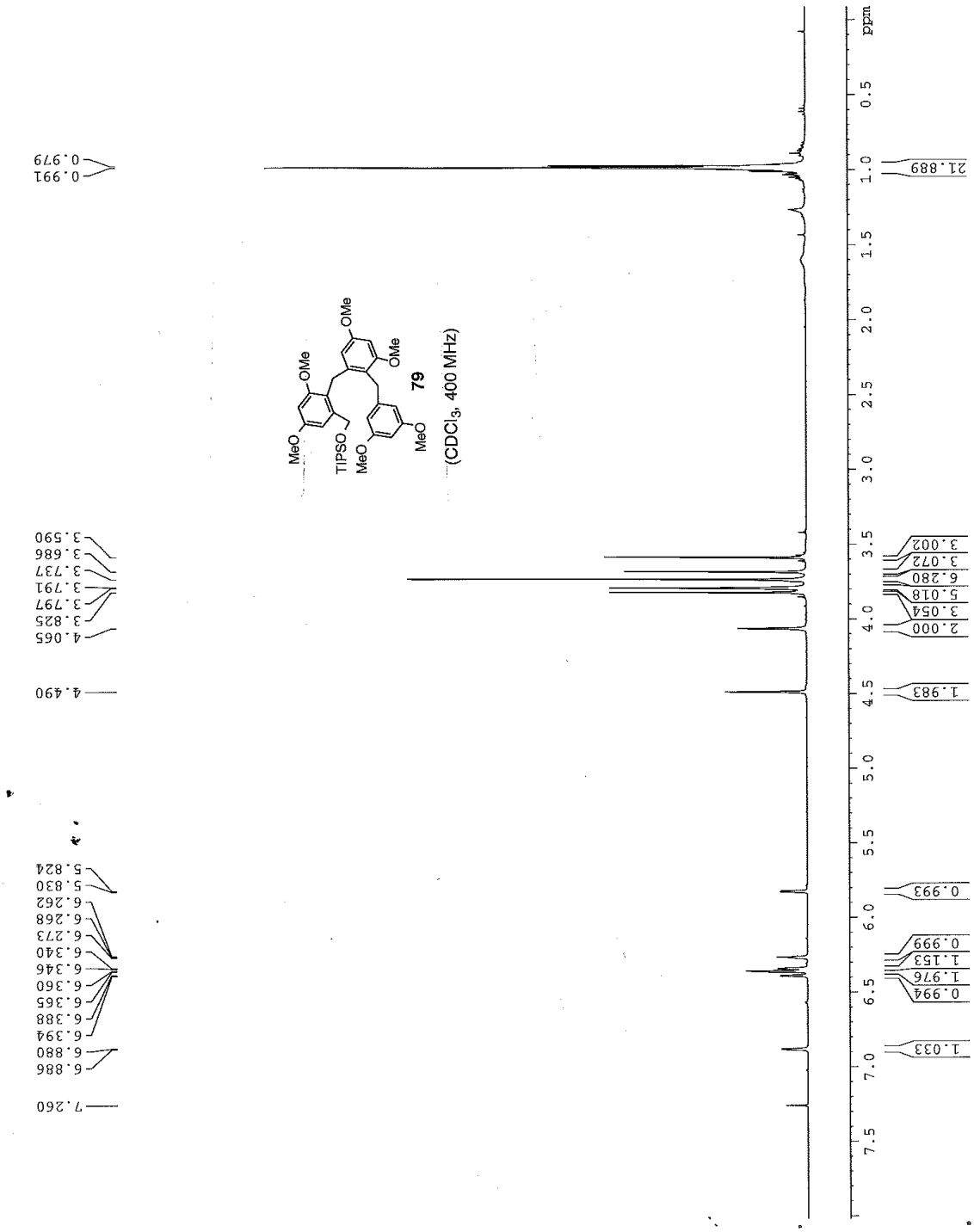
(CDCl3, 125 MHz)
ppm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6.340
6.346
6.360
6.365
6.388
6.394
6.880
6.886
7.260
21.889
1.033
0.994
1.976
1.153
0.999
0.993
1.983
2.000
3.054
5.018
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ppm
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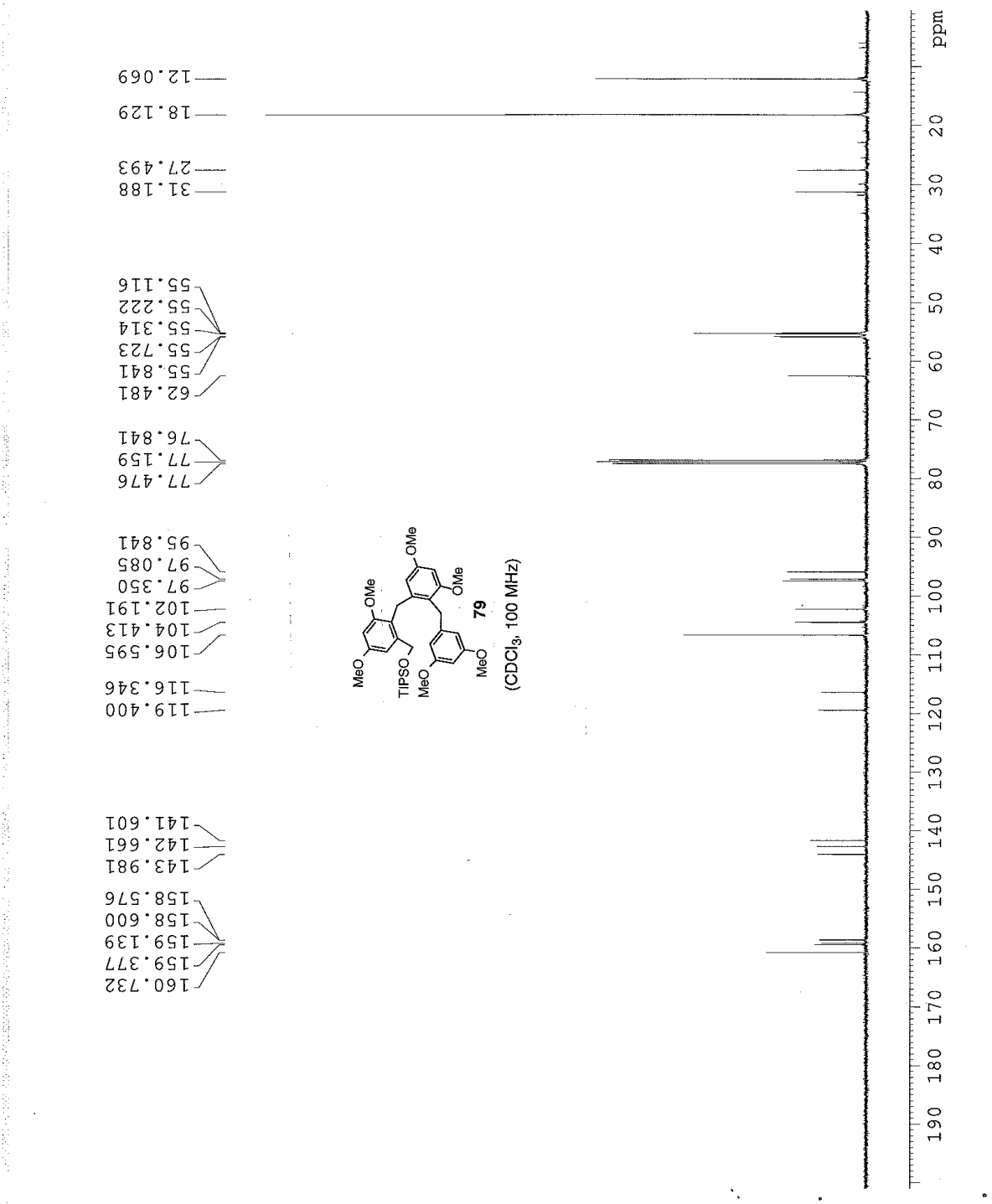
OMe
OMe
MeO
79
(CDCl3, 400 MHz)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95.841
97.085
97.350
102.191
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106.595
116.346
119.400
141.601
142.661
143.981
158.576
158.600
159.139
159.377
160.732
OMe
OMe
OMe
MeO
TIPSO
MeO
MeO
79
(CDCl3, 100 MHz)
ppm
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170
160
150
140
130
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110
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90
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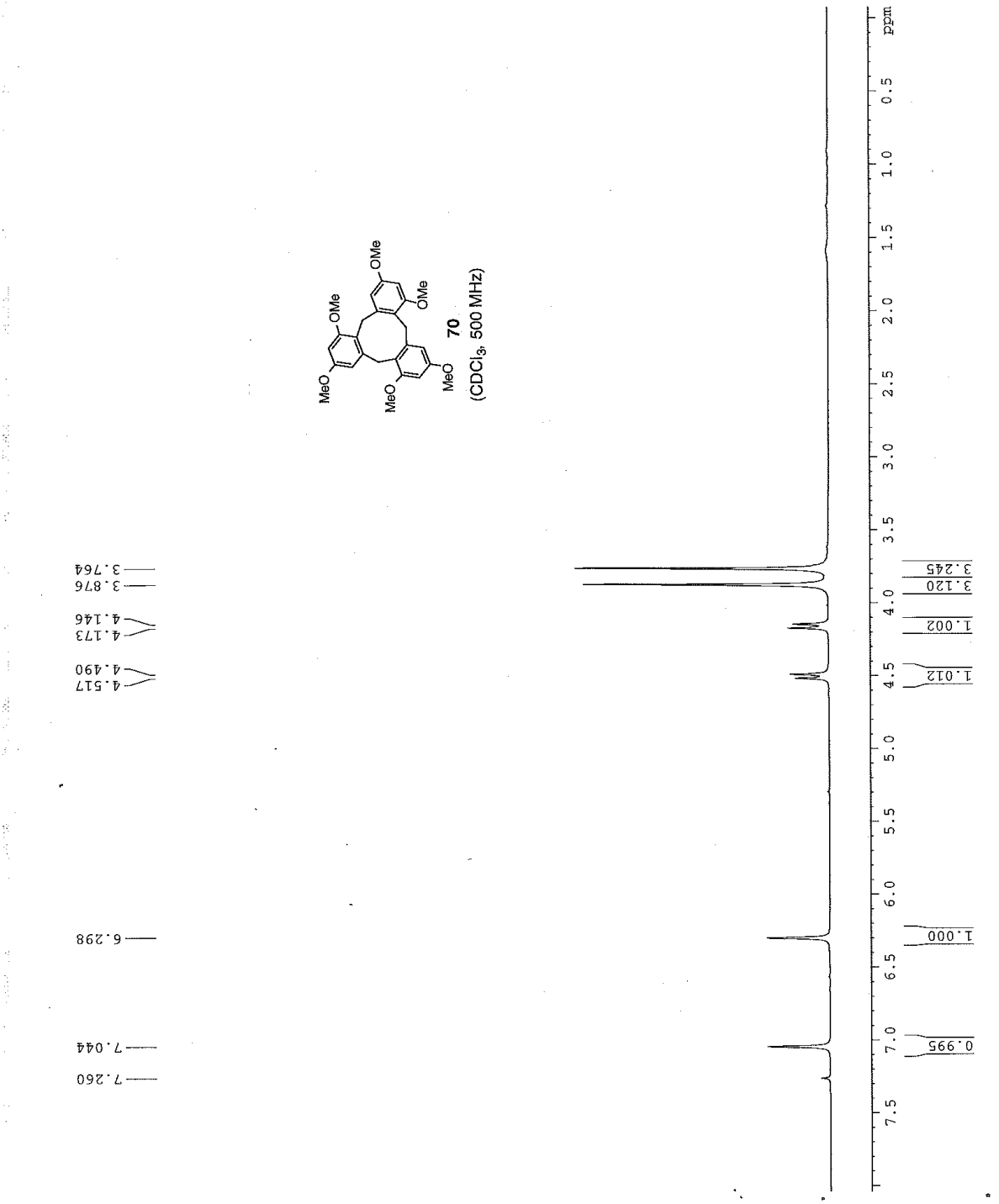
70
60
50
40
30
20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MeO
MeO
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3.120
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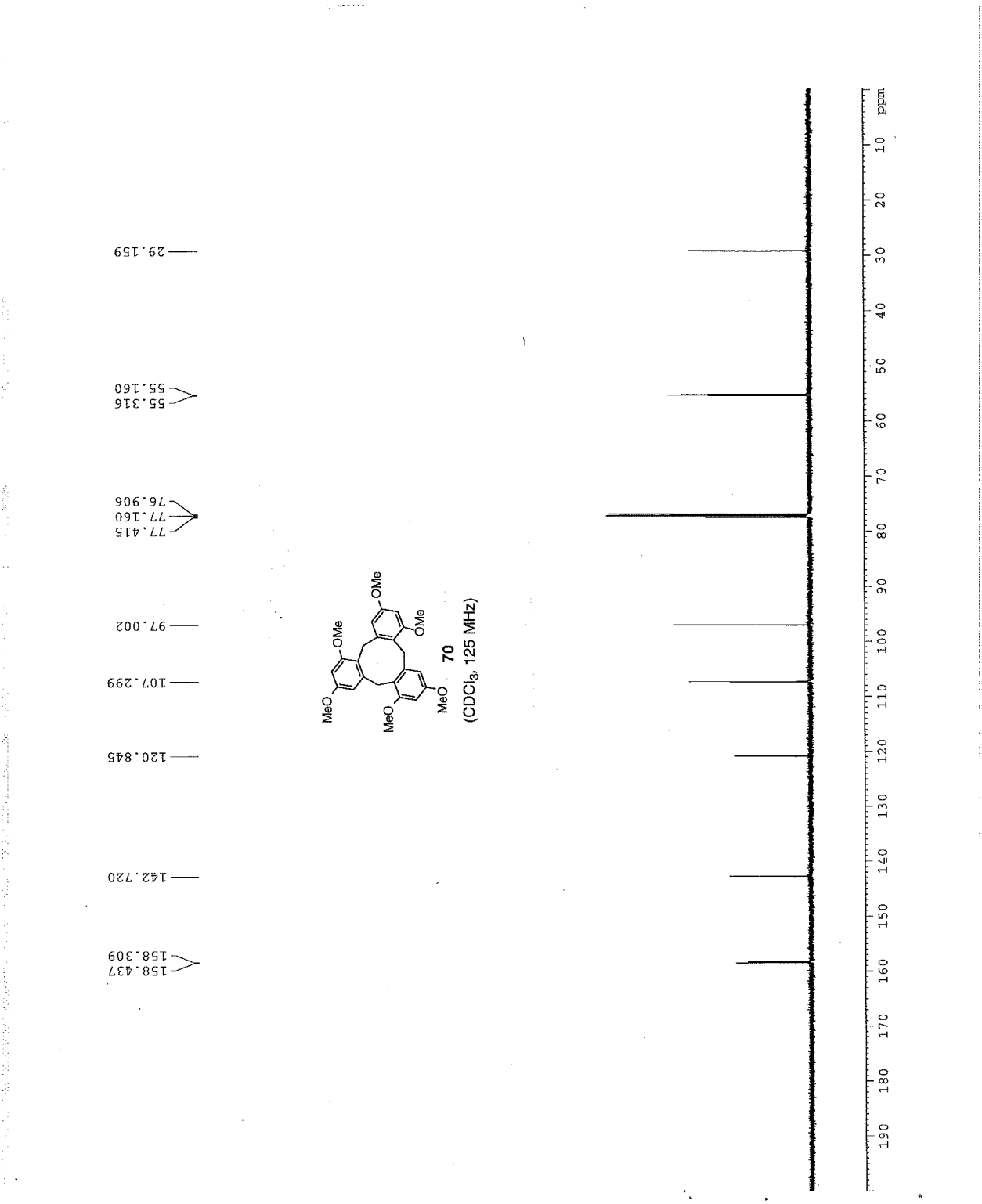
ppm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OMe
MeO
OMe
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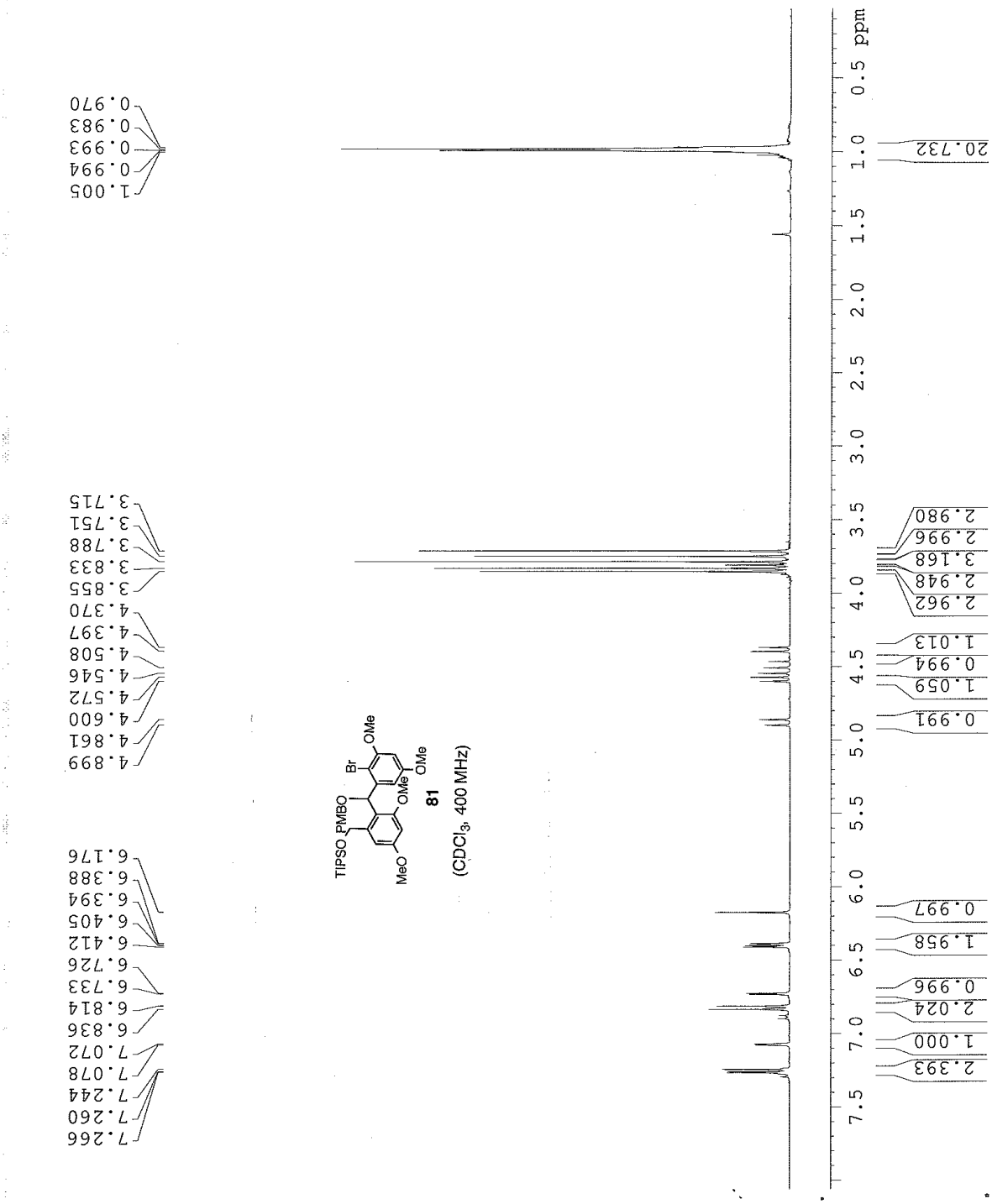
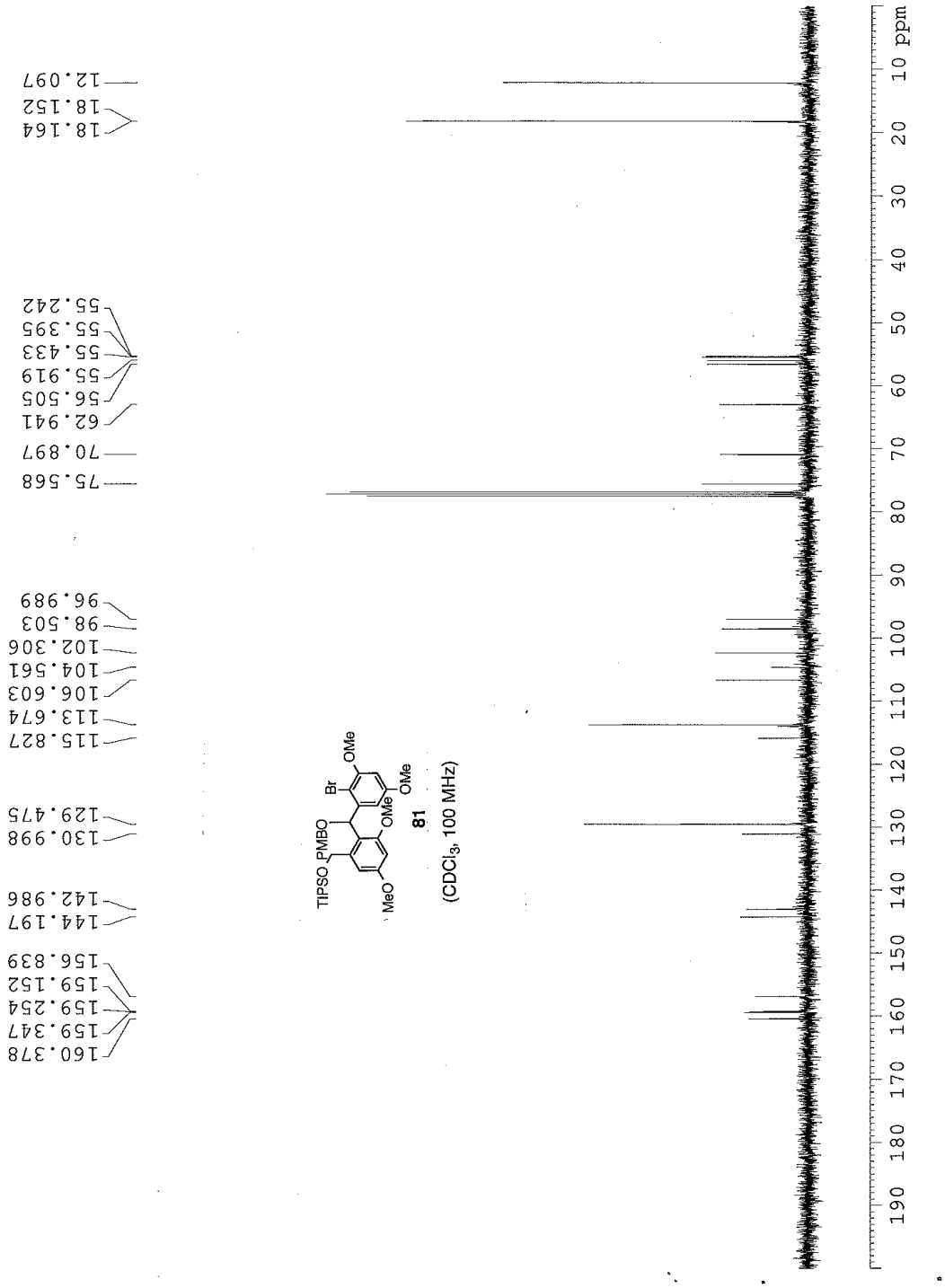
(CDCl3, 125 MHz)
ppm


TIPSO PMBO
Br
OMe
OMe
OMe
MeO
81
(CDCl3, 400 MHz)
ppm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102.306
104.561
106.603
113.674
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129.475
130.998
142.986
144.197
156.839
159.152
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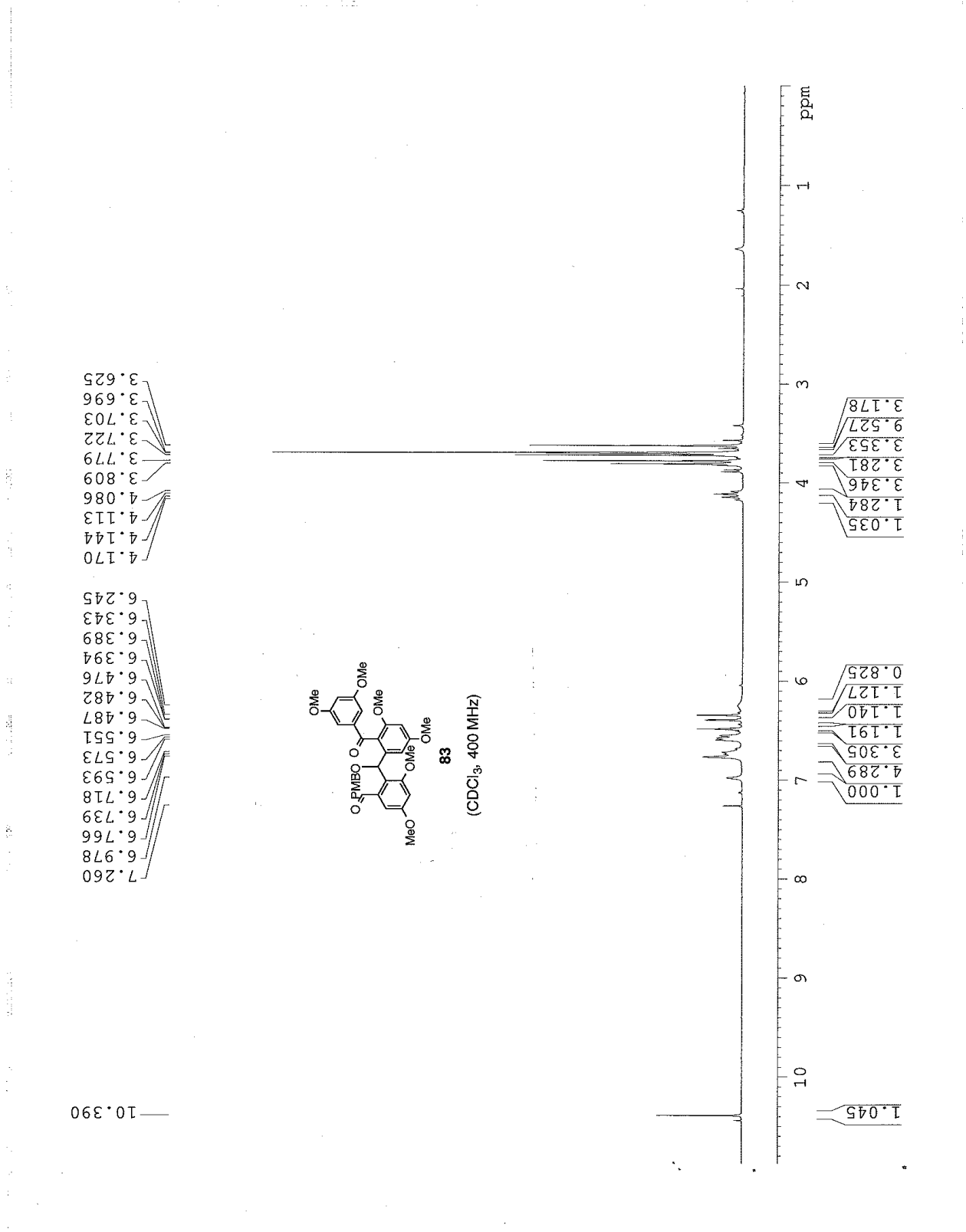
TIPSO
PMBO
Br
OMe
OMe
OMe
MeO
81
(CDCl3, 100 MHz)
10 ppm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6.476
6.394
6.389
6.343
6.245
4.170
4.144
4.113
4.086
3.809
3.779
3.722
3.703
3.696
3.625
1.045
1.000
4.289
3.305
1.191
1.140
1.127
0.825
1.035
1.284
3.346
3.281
3.353
9.527
3.178
ppm
1
2
3
4
5
6
7
8
9
10
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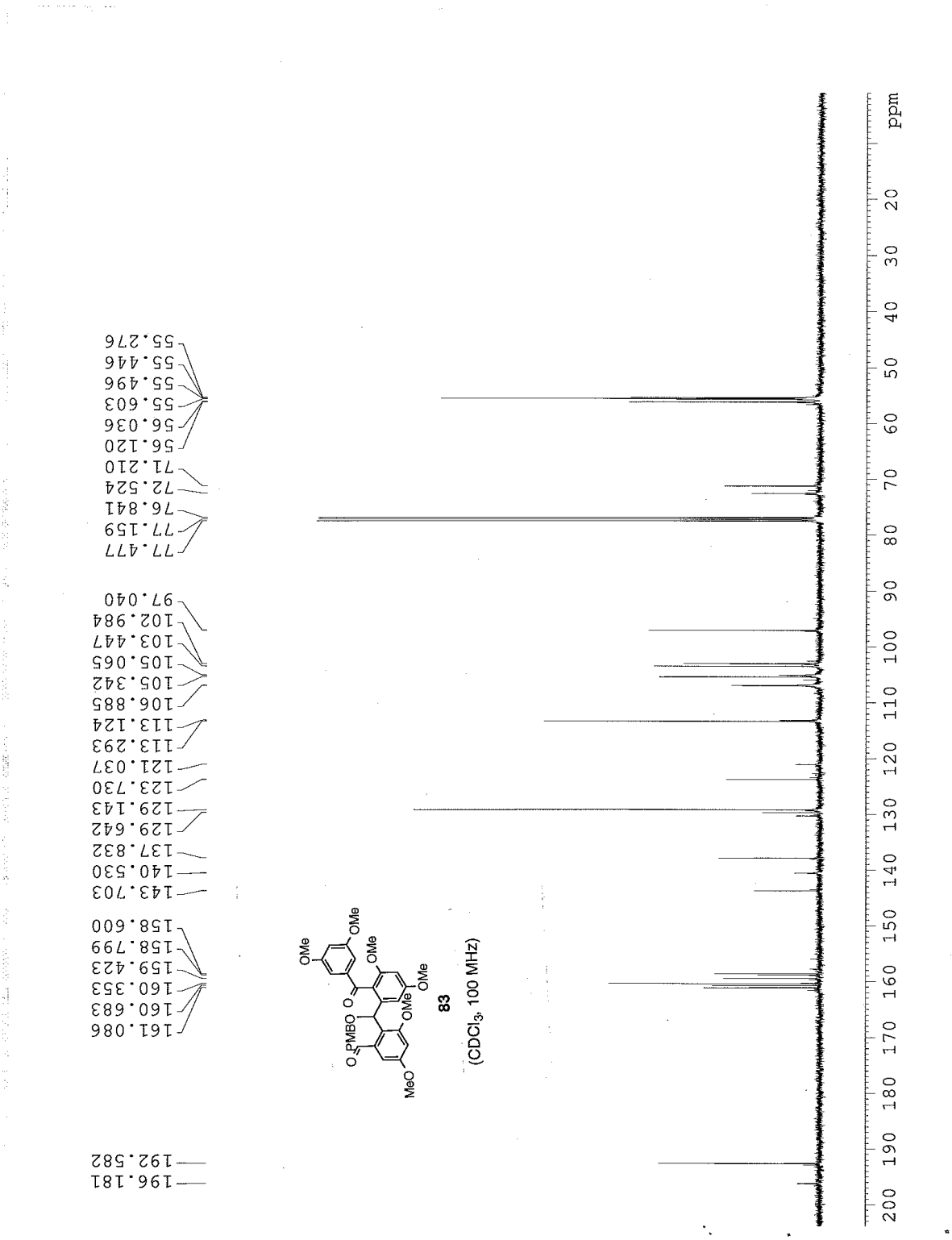
OMe
OMe
OMe
OMe
OMe
PMBO
O
O
MeO
83
(CDCl3, 400 MHz)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158.600
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129.143
123.730
121.037
113.293
113.124
106.885
105.342
105.065
103.447
102.984
97.040
77.477
77.159
76.841
72.524
71.210
56.120
56.036
55.603
55.496
55.446
55.276
OMe
OMe
OMe
OMe
OMe
PMBO
O
O
MeO
83
(CDCl3, 100 MHz)
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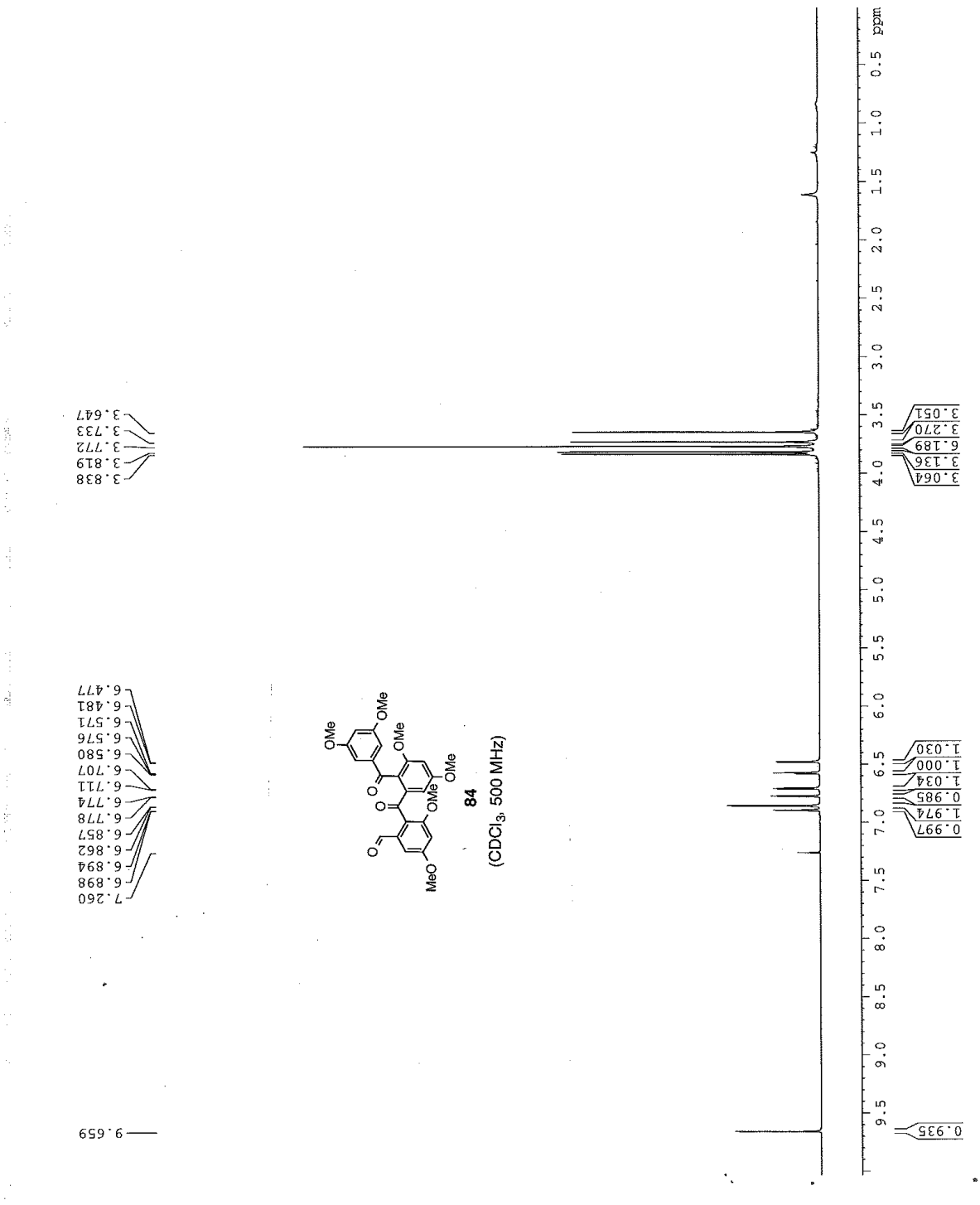
ppm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6.571
6.481
6.477
3.838
3.819
3.772
3.733
3.647
OMe
OMe
OMe
OMe
OMe
MeO
O
O
O
84
(CDCl3, 500 MHz)
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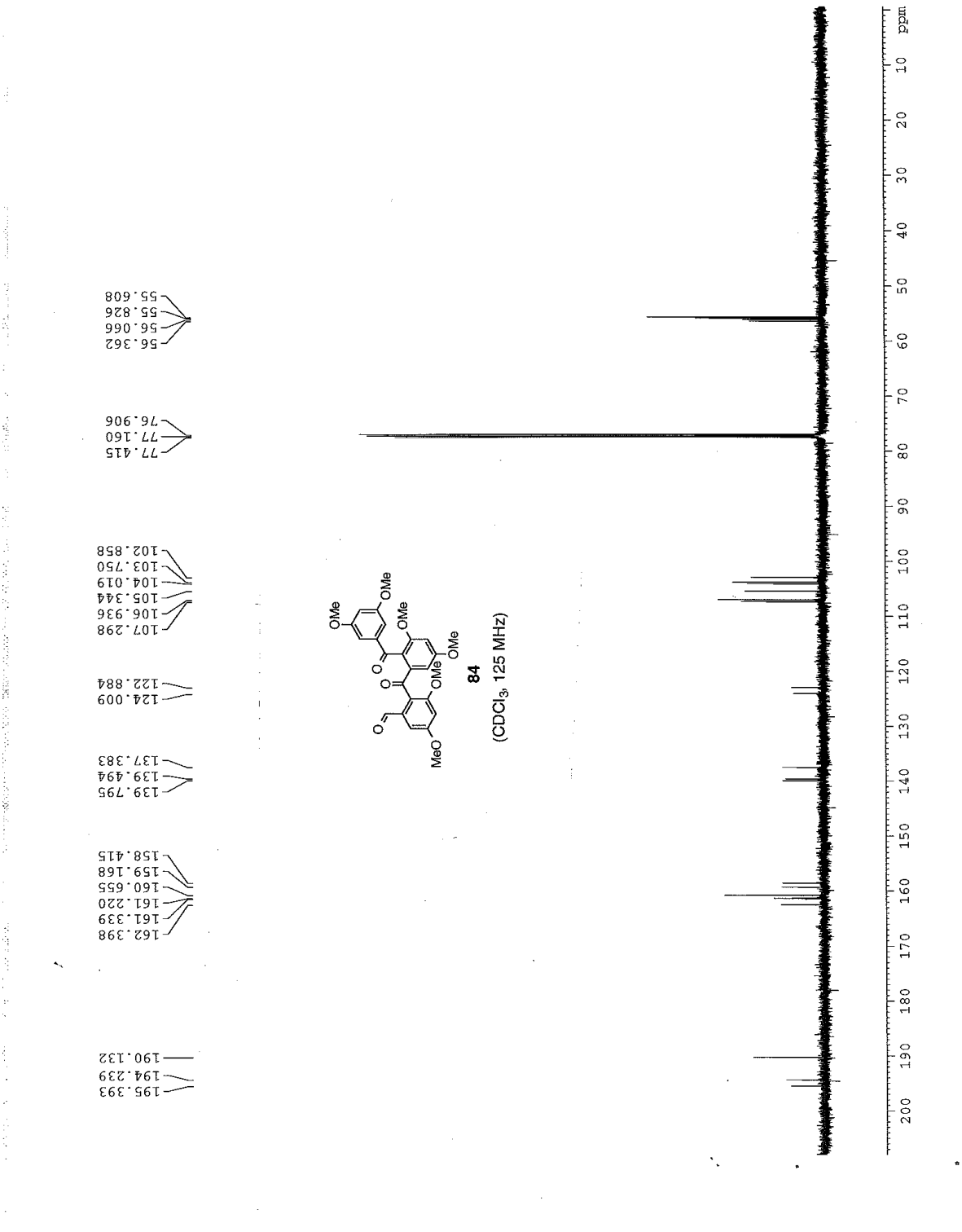
ppm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122.884
107.298
106.936
105.344
104.019
103.750
102.858
77.415
77.160
76.906
56.362
56.066
55.826
55.608
OMe
OMe
OMe
OMe
OMe
MeO
O
O
O
84
(CDCl3, 125 MHz)
ppm
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150
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80
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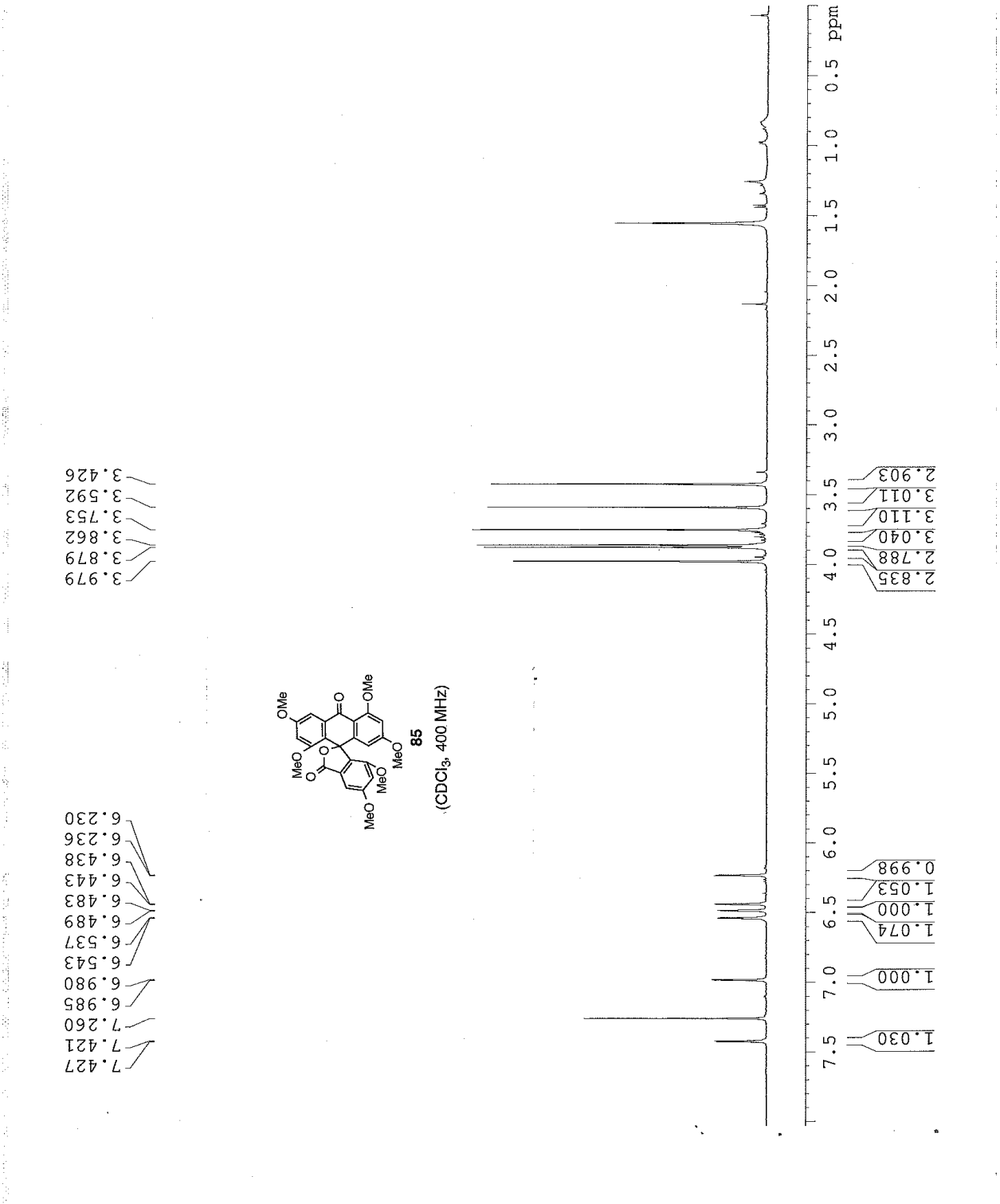
10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6.230
3.979
3.879
3.862
3.753
3.592
3.426
OMe
OMe
MeO
MeO
MeO
MeO
O
O
O
85
(CDCl3, 400 MHz)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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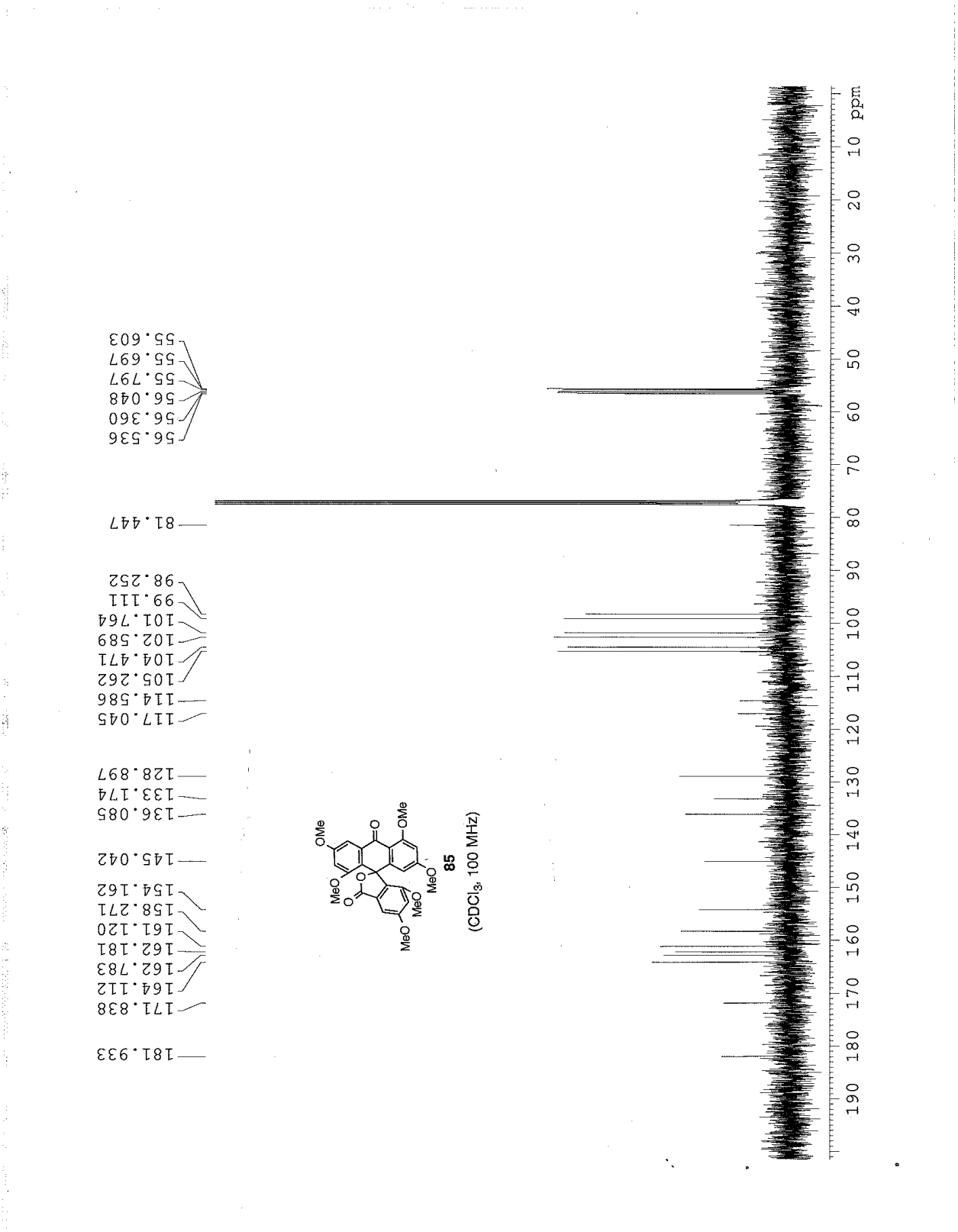
2.903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104.471
105.262
114.586
117.045
128.897
133.174
136.085
145.042
154.162
158.271
161.120
162.181
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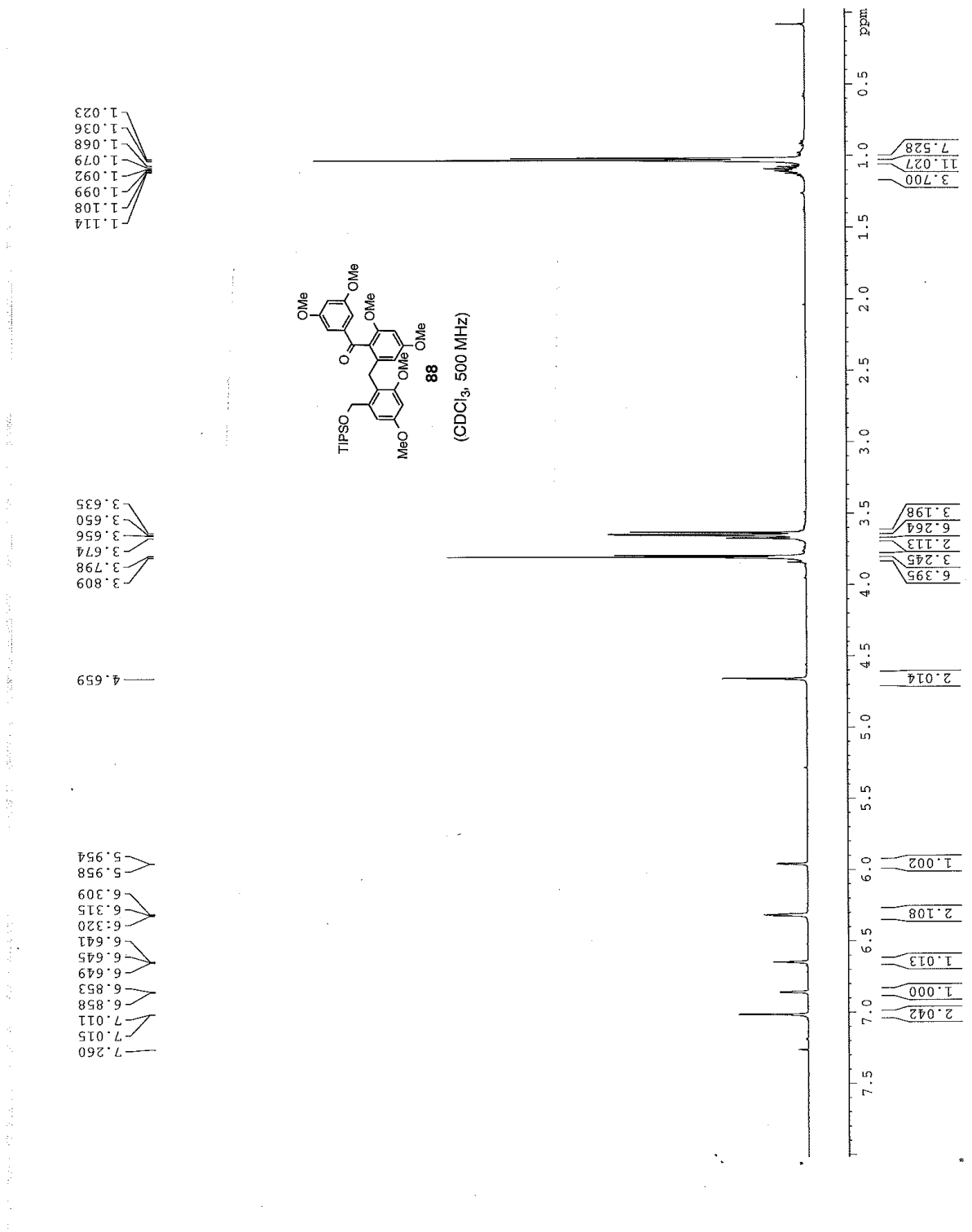
MeO
MeO
MeO
85
(CDCl3, 100 MHz)
ppm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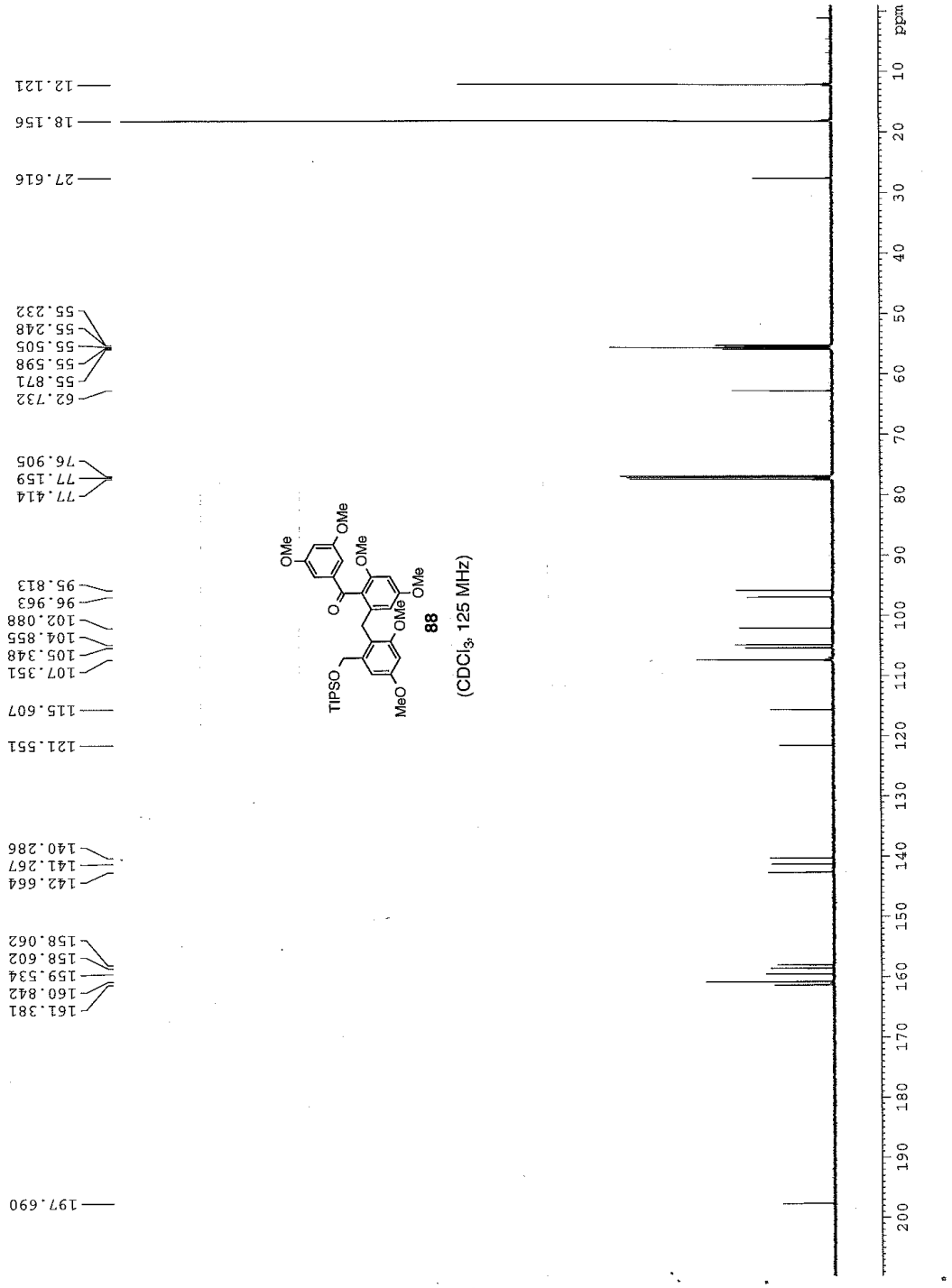
(CDCl3, 500 MHz)
TIPSO
MeO
OMe
ppm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96.963
102.088
104.855
105.348
107.351
115.607
121.551
140.286
141.267
142.664
158.062
158.602
159.534
160.842
161.381
197.690
OMe
OMe
OMe
OMe
OMe
TIPSO
MeO
O
88
(CDCl3, 125 MHz)
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
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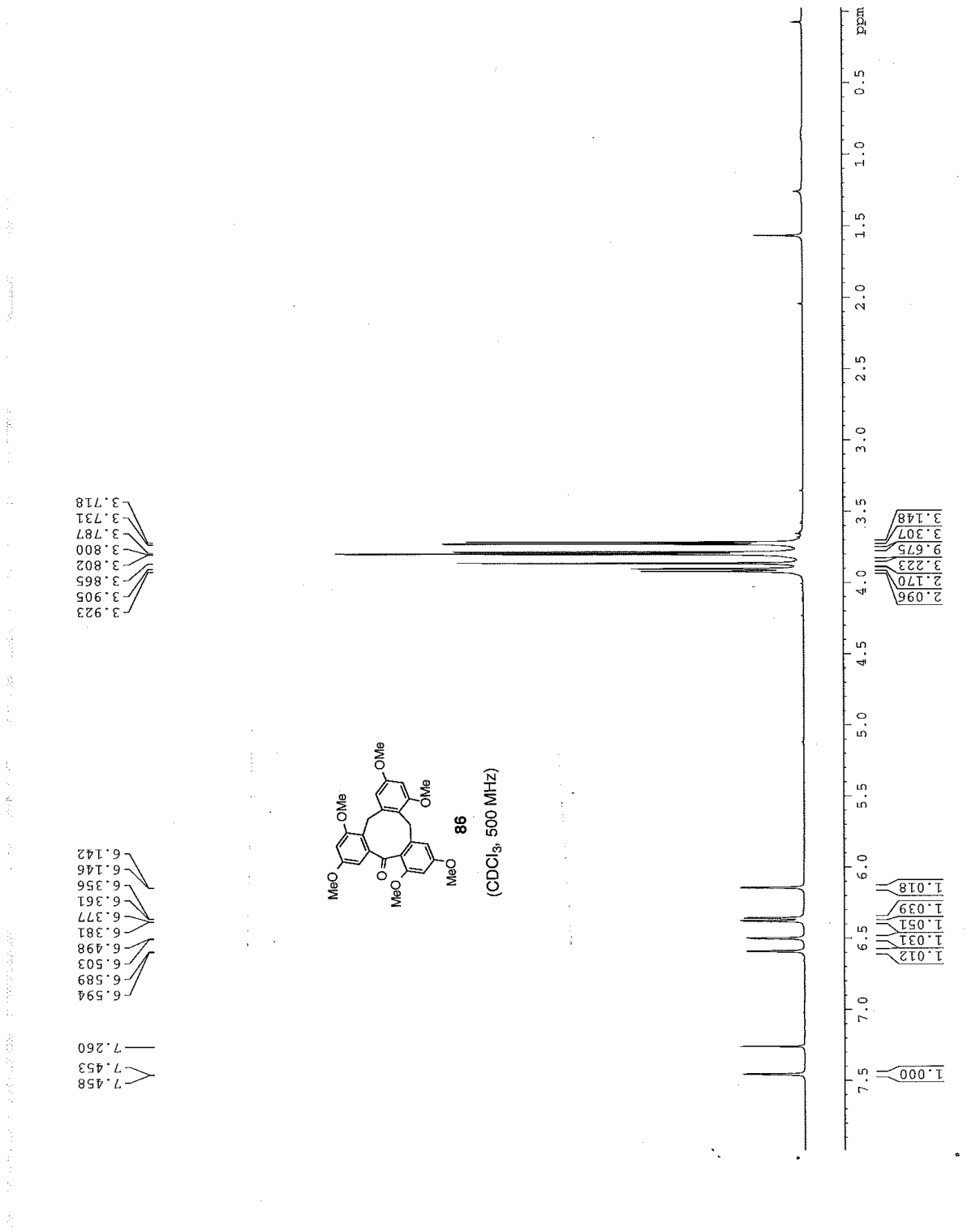
160
170
180
190
200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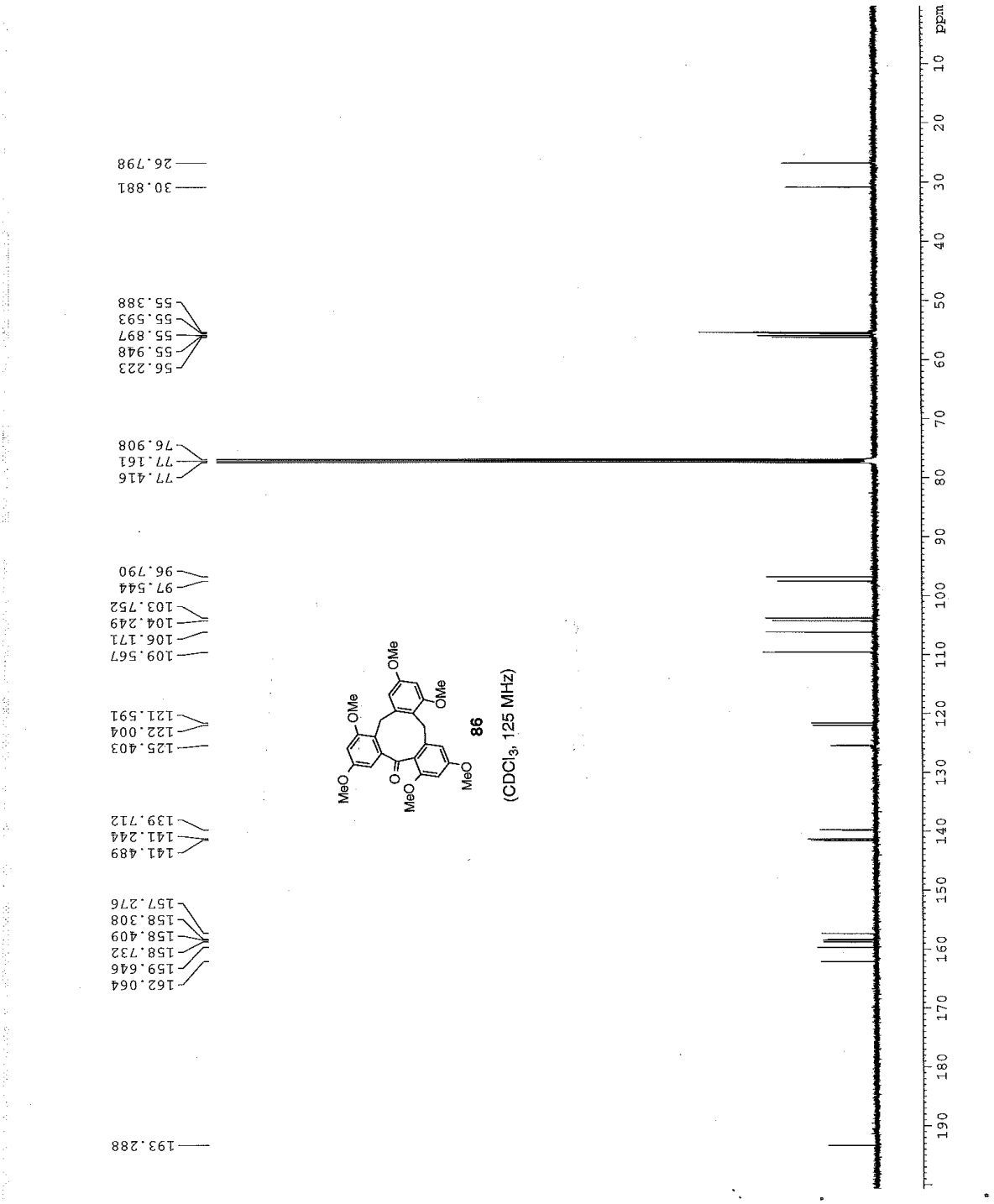
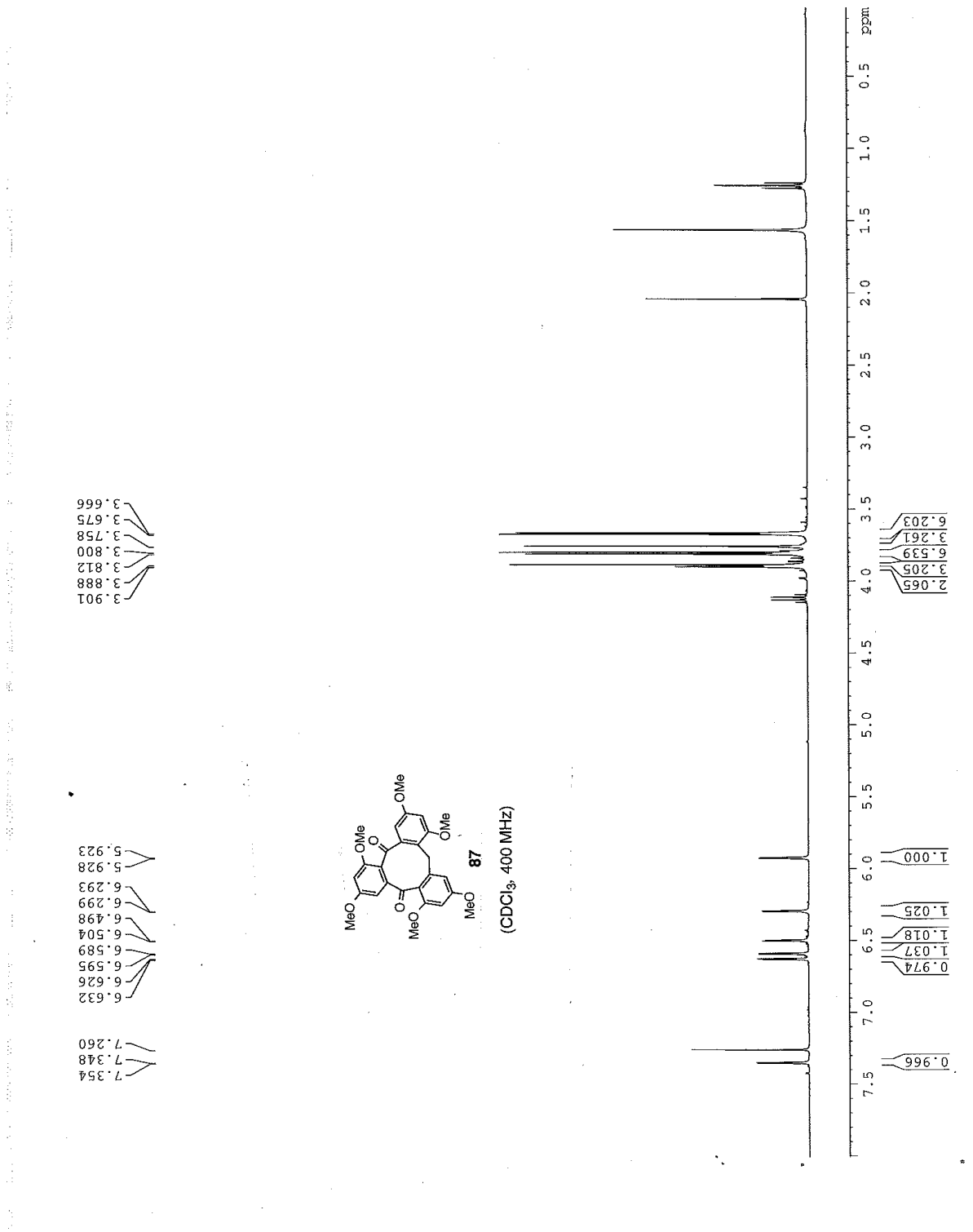
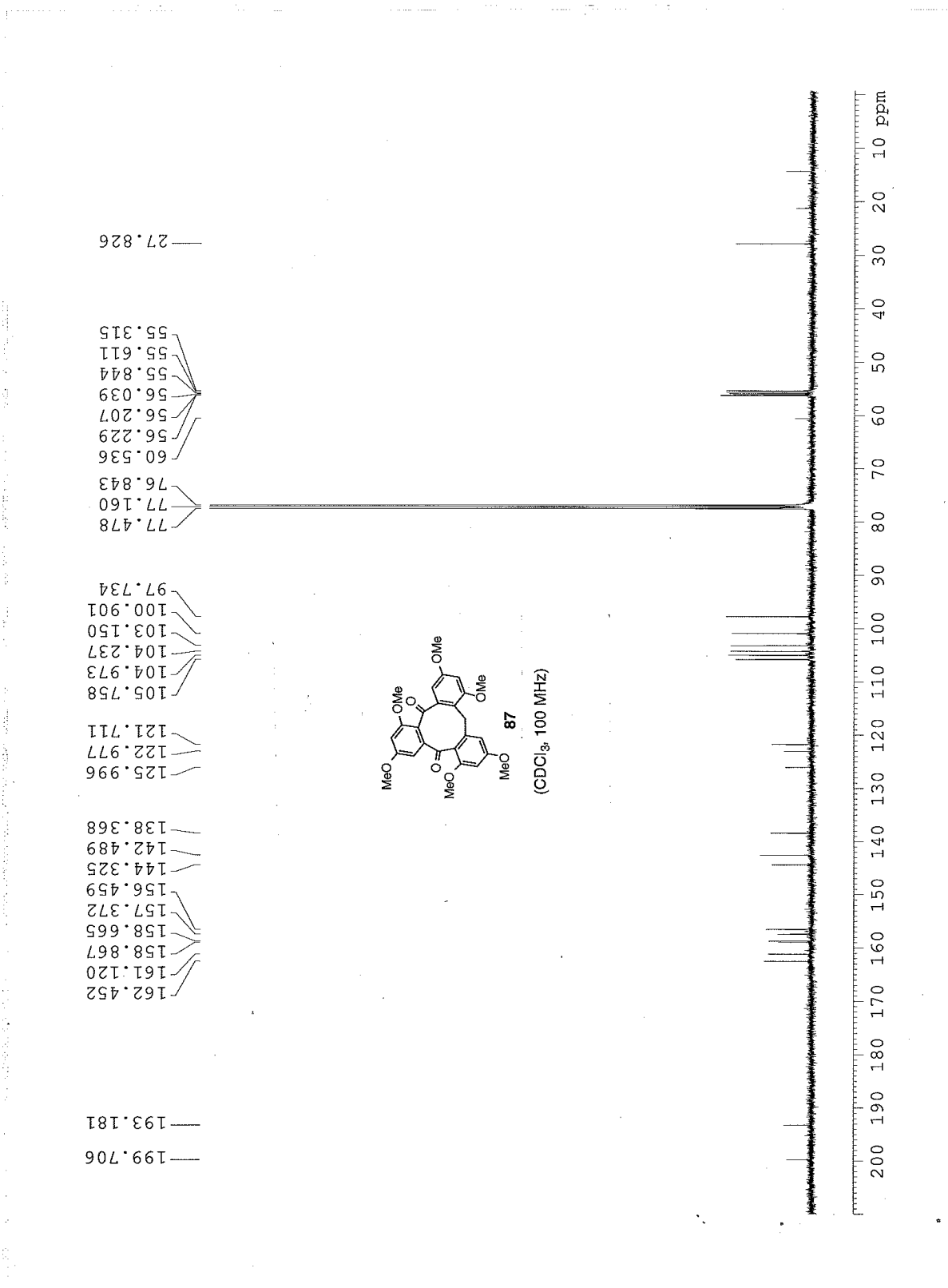
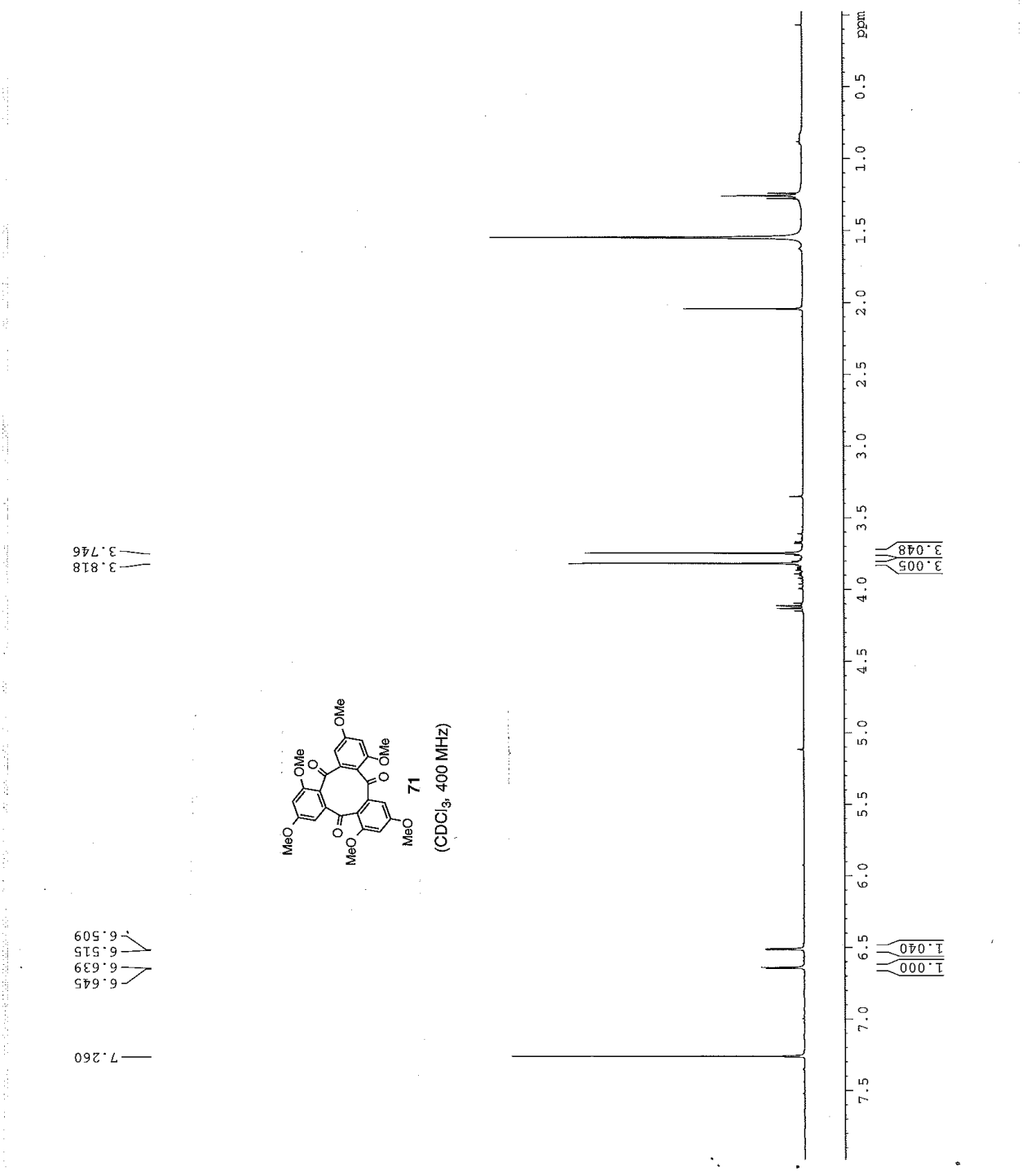
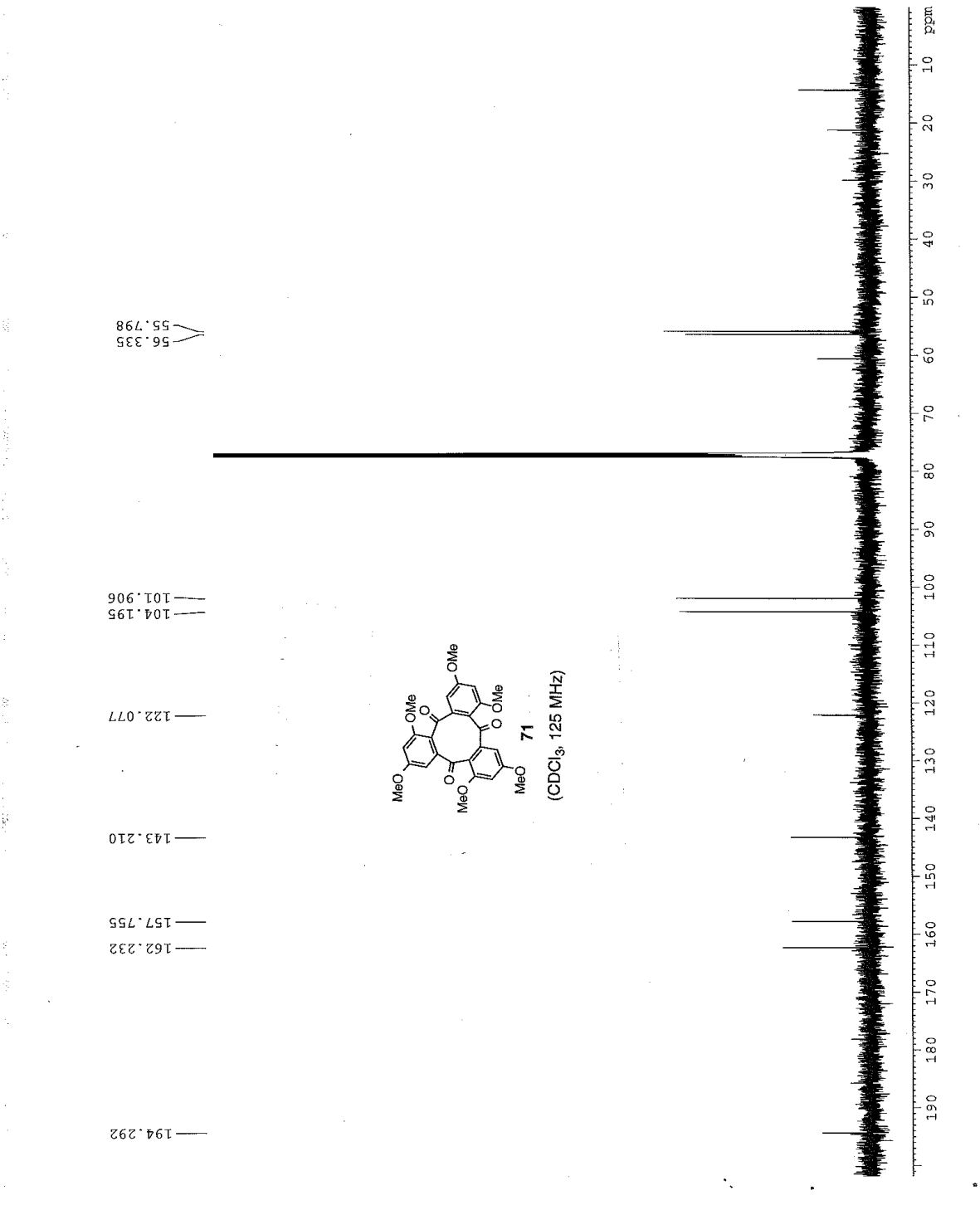
3.905
3.865
3.802
3.800
3.787
3.731
3.718
OMe
OMe
OMe
MeO
MeO
MeO
O
86
(CDCl3, 500 MHz)
1.000
1.012
1.031
1.051
1.039
1.018
2.096
2.170
3.223
9.675
3.307
3.148
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

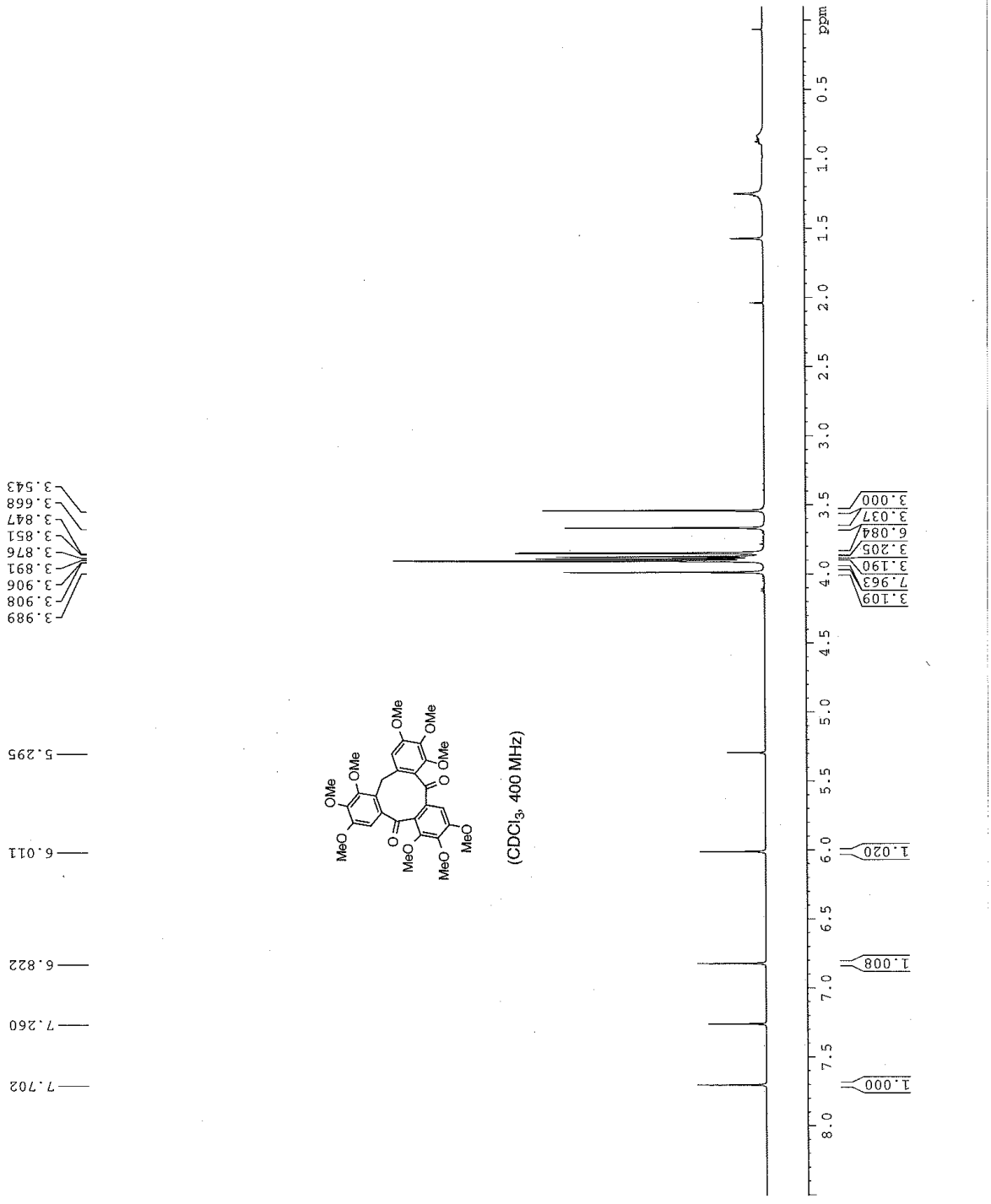

193.288
162.064
159.646
158.732
158.409
158.308
157.276
141.489
141.244
139.712
125.403
122.004
121.591
109.567
106.171
104.249
103.752
97.544
96.790
77.416
77.161
76.908
56.223
55.948
55.897
55.593
55.388
30.881
26.798
OMe
OMe
OMe
MeO
MeO
MeO
O
86
(CDCl3, 125 MHz)
ppm

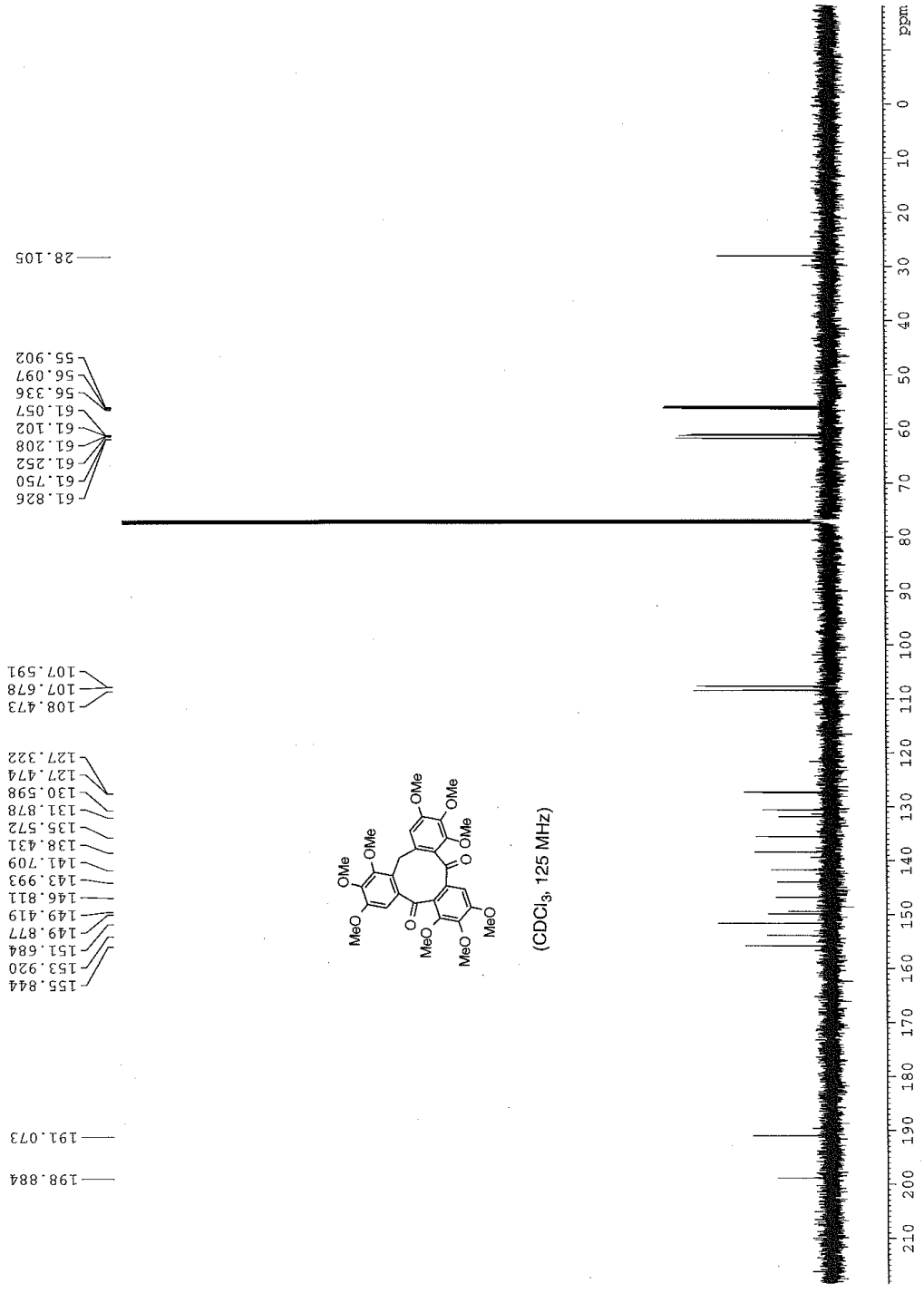

7.354
7.348
7.260
6.632
6.626
6.595
6.589
6.504
6.498
6.299
6.293
5.928
5.923
3.901
3.888
3.812
3.800
3.758
3.675
3.666
OMe
MeO
87
(CDCl3, 400 MHz)
0.966
1.000
1.025
1.018
1.037
0.974
2.065
3.205
6.539
3.261
6.203
ppm

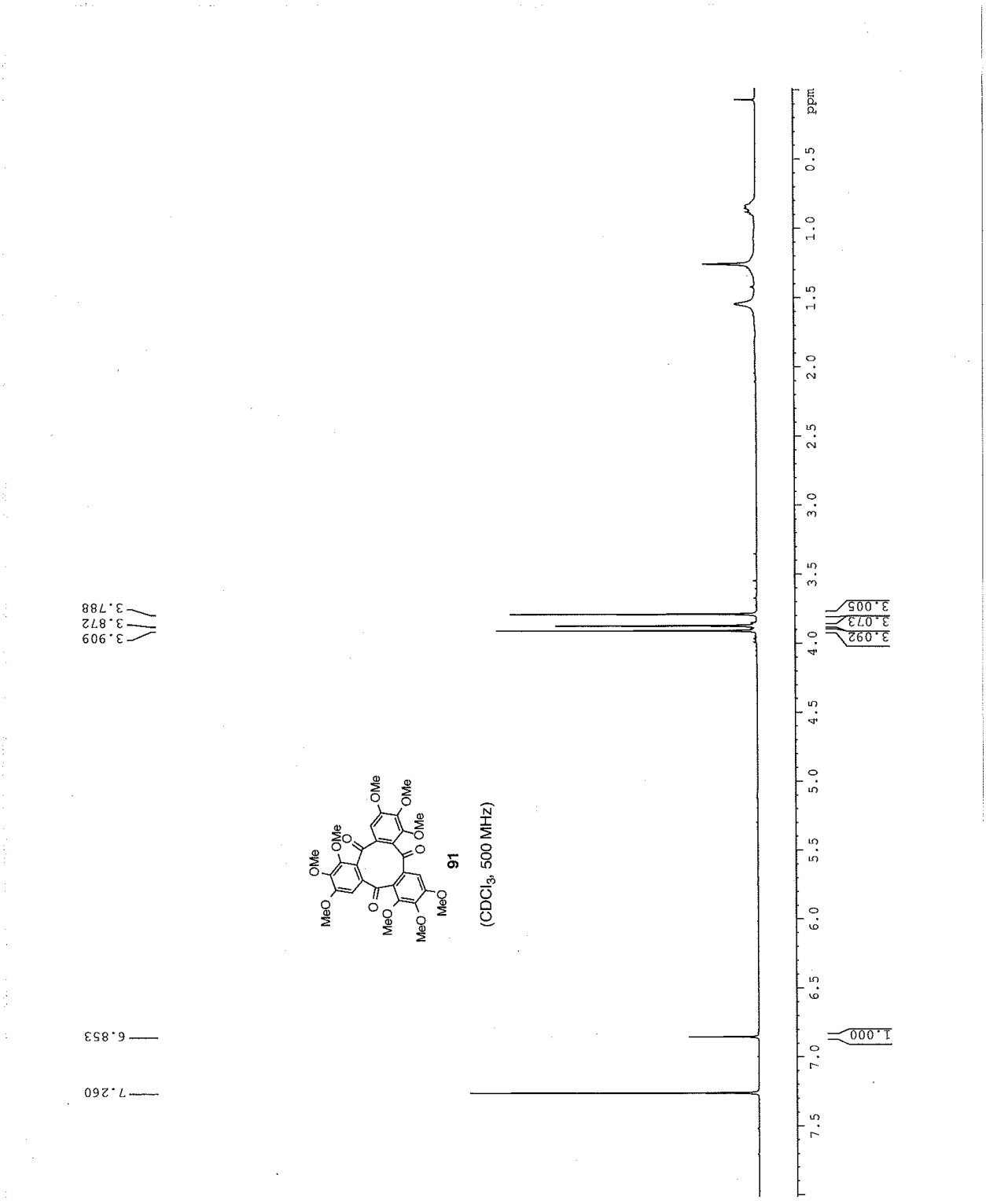

27.826
55.315
55.611
55.844
56.039
56.207
56.229
60.536
76.843
77.160
77.478
97.734
100.901
103.150
104.237
104.973
105.758
121.711
122.977
125.996
138.368
142.489
144.325
156.459
157.372
158.665
158.867
161.120
162.452
193.181
199.706
OMe
OMe
OMe
MeO
MeO
MeO
O
O
87
(CDCl3, 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

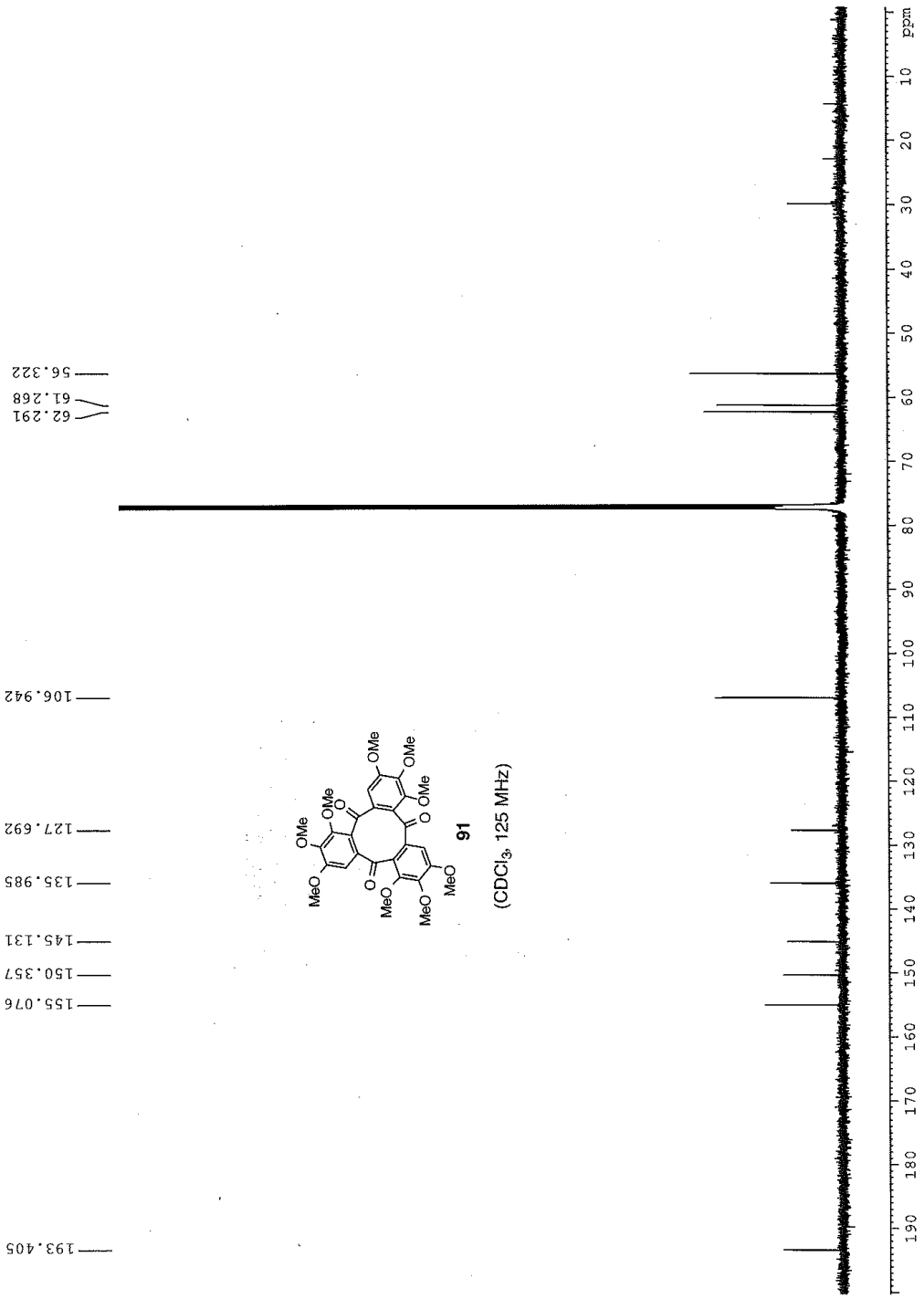

7.260
6.645
6.639
6.515
6.509
3.818
3.746
OMe
MeO
MeO
MeO
OMe
OMe
71
(CDCl3, 400 MHz)
1.000
1.040
3.005
3.048
ppm


194.292
162.232
157.755
143.210
122.077
104.195
101.906
56.335
55.798
MeO
OMe
MeO
OMe
MeO
OMe
71
(CDCl3, 125 MHz)
ppm


7.702
7.260
6.822
6.011
5.295
3.989
3.908
3.906
3.891
3.876
3.851
3.847
3.668
3.543
OMe
OMe
OMe
OMe
OMe
MeO
MeO
MeO
MeO
O
O
(CDCl3, 400 MHz)
1.000
1.008
1.020
3.109
7.963
3.190
3.205
6.084
3.037
3.000
ppm


198.884
191.073
155.844
153.920
151.684
149.877
149.419
146.811
143.993
141.709
138.431
135.572
131.878
130.598
127.474
127.322
108.473
107.678
107.591
61.826
61.750
61.252
61.208
61.102
61.057
56.336
56.097
55.902
28.105
(CDCl3, 125 MHz)
ppm


3.909
3.872
3.788
7.260
6.853
1.000
3.092
3.073
3.005
ppm
MeO
OMe
O
91
(CDCl3, 500 MHz)


193.405
155.076
150.357
145.131
135.985
127.692
106.942
62.291
61.268
56.322
OMe
MeO
91
(CDCl3, 125 MHz)
ppm